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 MBräun 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

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<th>Abbreviation</th>
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<tr>
<td>4-DMAP</td>
<td>4-Dimethylaminopyridine</td>
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<td>9-Borabicyclo(3.3.1)nonane</td>
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**Hex-5-enoic acid 19**

[Image of Hex-5-enoic acid]

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$_2$SO$_4$ 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$_3$) $\delta$ = 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$_3$) $\delta$ = 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$_6$H$_9$O$_2$ [M-H]: 113.0608; found: 113.0604.

**nBuLi (1.6 M in hexanes, 126 mL, 200.4 mmol, 1.2 eq) was added to a solution of (4R)-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. NH₄Cl solution (500 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with sat. NaHCO₃ solution (500 mL), sat. NH₄Cl solution (500 mL) and brine (500 mL), dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo. Purification by column chromatography (EtOAc/Pet. ether 1:9) gave (4R)-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; [α]D -30.6° (c 1.46, CHCl₃) [lit.² (4S)-21 [α]D +33.1° (c 1.0, CHCl₃)]; ¹H NMR (500 MHz, CDCl₃) δ = 0.94 (3H, d, J(H,H)= 6.8 Hz, CH₃), 1.02 (3H, d, J(H,H)= 7.0 Hz, CH₃), 1.37 (3H, s, CH₃), 1.51 (3H, s, CH₃), 1.72-1.86 (2H, m, CH₂), 2.11-2.16 (3H, m, CH₂, CH), 2.89 (1H, ddd, J(H,H)= 16.7, 8.6, 6.4 Hz, CH₃H), 3.02 (1H, ddd, J(H,H)= 16.7, 8.6, 6.4 Hz, CH₃H), 4.15 (1H, d, J(H,H)= 3.3 Hz, CH), 5.02 (2H, dddd, J(H,H)= 31.3, 16.7, 8.6, 6.3 Hz, CH₂H), 5.77-5.85 (1H, m, CH); ¹³C NMR (125 MHz, CDCl₃) δ = 17.3 (CH₃), 21.6 (CH₃), 21.7 (CH₃), 24.0 (CH₂), 29.0 (CH₃), 29.8 (CH), 33.3 (CH₂), 35.0 (CH₂), 66.4 (CH), 82.9 (C), 115.5 (CH₂), 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 C₁₄H₂₃N₁Na₁O₃ [M+Na]⁺: 276.1570; found: 276.1562.

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

NaHMDS (1.0 M in THF, 120 mL, 120 mmol, 1.1 eq) was added to a solution of (4R)-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. NH₄Cl solution (250 mL) and extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with sat. NaHCO₃ solution (250 mL), sat. NH₄Cl solution (250 mL) and brine (250 mL), dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo. Purification by column chromatography (EtOAc/Pet. ether 1:9) gave (4R)-5,5-dimethyl-3-((2R)-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; [α]D -52.8° (c 1.23,
CHCl₃ [lit.² (2S,4S)-22 [α]D +51.4° (c 1.0, CHCl₃)]; ¹H NMR (500 MHz, CDCl₃) δ = 0.96 (3H, d, J(H,H)= 6.8 Hz, CH₃), 1.02 (3H, d, J(H,H)= 6.9 Hz, CH₃), 1.27 (3H, d, J(H,H)= 6.8 Hz, CH₃), 1.38 (3H, s, CH₃), 1.46-1.52 (1H, m, CH₂), 1.52 (3H, s, CH₃), 1.85-1.92 (1H, m, CH₂), 2.04-2.09 (2H, m, CH₂), 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, 1.5 Hz, CH₂), 5.74-5.82 (1H, m, CH); ¹³C NMR (125 MHz, CDCl₃) δ = 17.1 (CH₃), 18.7 (CH₃), 21.6 (CH₃), 21.8 (CH₃), 28.9 (CH₃), 29.8 (CH), 31.9 (CH₂), 32.4 (CH₂), 37.5 (CH), 66.3 (CH), 82.8 (C), 115.2 (CH₂), 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 C₁₅H₂₅N₁Na₁O₃ [M+Na]⁺: 290.1727; found: 290.1720.

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

Lithium aluminium hydride (4.6 g, 122.1 mmol, 4.0 eq) was added to a solution of (4R)-5,5-dimethyl-3-((2R)-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 (2R)-2-methylhex-5-en-1-ol 23 (2.29 g, 66%) as a colourless oil; [α]D +10.0° (c 1.05, CHCl₃), lit.³ [α]D +9.1° (c 3.03, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ = 0.94 (3H, d, J(H,H)= 6.7 Hz, CH₃), 1.18-1.26 (1H, m, CH₂AB), 1.41 (1H, bs, OH), 1.49-1.56 (1H, m, CH₃AB), 1.61-1.72 (1H, m, CH), 2.02-2.18 (2H, m, CH₂), 3.45 (1H, dd, J(H,H)= 10.5, 6.4 Hz, CH₃AB), 3.52 (1H, dd, J(H,H)= 10.6, 5.8 Hz, CH₃AB), 4.94-5.05 (2H, m, CH₂), 5.78-5.86 (1H, m, CH); ¹³C NMR (125 MHz, CDCl₃) δ = 16.6 (CH₃), 31.4 (CH₂), 32.5 (CH₂), 35.4 (CH), 68.4 (CH₂), 114.6 (CH₂), 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 C₇H₁₅O₁ [M+H]⁺: 115.1117; found: 115.1115.
A solution of (2R)-2-methylhex-5-en-1-ol (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 ((2R)-2-methylhex-5-en-1-ol)oxy)methyl)benzene (3.68 g, 94%) as a colourless oil; \([\alpha]_D^\text{23} = -2.7^\circ\) (c 1.20, CHCl\(_3\)) [lit.\(^4\) (2S)-11 \([\alpha]_D^\text{21} = +2.6^\circ\) (c 6.2, CHCl\(_3\))];

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 0.95\) (3H, d, \(J(H,H)= 6.8\) Hz, CH\(_3\)), 1.19-1.27 (1H, m, CH\(_A\)H\(_B\)), 1.53-1.60 (1H, m, CH\(_A\)H\(_B\)), 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\(_A\)H\(_B\)), 3.35 (1H, dd, \(J(H,H)= 9.0, 6.0\) Hz, CH\(_A\)H\(_B\)), 4.50 (1H, d, \(J(H,H)= 12.3\) Hz, CH\(_A\)H\(_B\)), 4.53 (1H, d, \(J(H,H)= 12.3\) Hz, CH\(_A\)H\(_B\)), 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\(_3\)) \(\delta = 17.2\) (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) \(\nu\) (cm\(^{-1}\)) = 3065, 3030, 2928, 2854, 1461, 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\(_1\)O\(_1\) [M+Na]\(^{+}\): 227.1406; found: 227.1402.

Ozone was bubbled through a solution of (((2R)-2-methylhex-5-en-1-ol)oxy)methyl)benzene (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.

\((4R)-5-(Benzyloxy)-4-methylpentanal\)
Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (4R)-5-(benzyloxy)-4-methylpentanal 12 (1.93 g, 55%) as a colourless oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 0.95 (3H, d, $J$(H,H)= 6.5 Hz, CH$_3$), 1.47-1.55 (1H, m, CHA$_BH$), 1.77-1.87 (2H, m, CHA$_BH$, 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$_3$) $\delta$ = 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

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$_2$SO$_4$ 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$_3$) $\delta$ = 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$_3$) $\delta$ = 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) $\nu$ (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$_2$O$_2$ [M+Na]$^+$: 247.1305; found: 247.1297.

6-((4-Methoxyphenyl)methoxy)hexan-1-ol 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; 1H NMR (400 MHz, CDCl₃) δ = 1.35-1.44 (4H, m, CH₂), 1.46 (1H, bs, OH), 1.54-1.65 (4H, m, CH₂), 3.45 (2H, t, J(H,H)= 6.6 Hz, CH₂), 3.63 (2H, t, J(H,H)= 6.6 Hz, CH₂), 3.81 (3H, s, CH₃), 4.44 (2H, s, CH₂), 6.78-6.90 (2H, m, ArH), 7.25-7.29 (2H, m, ArH); 13C NMR (100 MHz, CDCl₃) δ = 25.8 (CH₂), 26.2 (CH₂), 29.9 (CH₂), 32.9 (CH₂), 55.5 (CH₃), 70.2 (CH₂), 72.7 (CH₂), 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 C₁₄H₂₂NaO₂ [M+Na]⁺: 261.1461; found: 261.1455.

5-((4-Methoxyphenyl)methoxy)pentanal 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 Na₂SO₄ 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; 1H NMR (400 MHz, CDCl₃) δ = 1.56-1.78 (4H, m, CH₂), 2.46 (2H, dt, J(H,H)= 7.3, 1.7 Hz, CH₂), 3.46 (2H, t, J(H,H)= 6.0 Hz, CH₂), 3.81 (3H, s, CH₃), 4.43 (2H, s, CH₂), 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); 13C NMR (100 MHz, CDCl₃) δ = 19.2 (CH₂), 29.3 (CH₂), 43.8 (CH₂), 55.5 (CH₃), 69.6 (CH₂), 72.8 (CH₂), 114.0 (CH), 129.5 (CH), 130.7 (C), 159.3 (C), 202.8 (CHO).

6-((4-Methoxyphenyl)methoxy)hexanal 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. NaHCO₃ 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 Na₂SO₄ 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; ¹H NMR (400 MHz, CDCl₃) δ = 1.38-1.46 (2H, m, CH₂), 1.56-1.69 (4H, m, CH₂), 2.44 (2H, dt, J(H,H)= 7.4, 1.8 Hz, CH₂), 3.45 (2H, t, J(H,H)= 6.5 Hz, CH₂), 3.81 (3H, s, CH₃), 4.43 (2H, s, CH₂), 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); ¹³C NMR (100 MHz, CDCl₃) δ = 22.1 (CH₂), 26.1 (CH₂), 29.7 (CH₂), 44.1 (CH₂), 55.5 (CH₃), 69.9 (CH₂), 72.8 (CH₂), 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

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. NH₄Cl 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 Na₂SO₄ 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; ¹H NMR (500 MHz, CDCl₃) δ = 1.52-1.79 (8H, m, CH₂), 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\(_3\)) \(\delta = 22.0\) (\(CH_2\)), 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) \(\nu (cm^{-1}) = 3406, 3290, 2941, 2863, 1612, 1586, 1513, 1464, 1303, 1248, 1174, 1094, 1034, 821, 638\); MS (ESI) 271 (100) [M+Na]\(^+\); HRMS: \(m/z\) calcd for C\(_{15}\)H\(_{20}\)NaO\(_3\) [M+Na]\(^+\): 271.1305; found: 271.1299.

8-((4-Methoxyphenyl)methoxy)oct-1-yn-3-ol 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\(_3\)) \(\delta = 1.38-1.52\) (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\(_3\)) \(\delta = 25.0\) (\(CH_2\)), 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) \(\nu (cm^{-1}) = 3398, 3289, 2939, 2861, 2092, 1681, 1612, 1513, 1464, 1303, 1249, 1174, 1090, 1034, 821, 643\); MS (ESI) 285 (100) [M+Na]\(^+\), 121 (30); HRMS: \(m/z\) calcd for C\(_{16}\)H\(_{22}\)NaO\(_3\) [M+Na]\(^+\): 285.1461; found: 285.1454.

7-((4-Methoxyphenyl)methoxy)hept-1-yn-3-one 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$_2$SO$_4$ 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$_3$) $\delta$ = 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$_2$), 6.82-6.91 (2H, m, ArH), 7.27-7.28 (2H, m, ArH); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 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) $\nu$ (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: $m/z$ caled for C$_{16}$H$_{18}$Na$_1$O$_3$ [M+Na]$^+$: 269.1148; found: 269.1141.

8-((4-Methoxyphenyl)methoxy)oct-1-yn-3-one 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$_3$) $\delta$ = 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$_3$) $\delta$ = 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) $\nu$ (cm$^{-1}$) = 3259, 2938, 2862, 2092, 1683, 1613, 1513, 1248, 1100, 1034, 821; MS (ESI) 283 (100) [M+Na]$^+$; HRMS: $m/z$ caled for C$_{16}$H$_{20}$Na$_1$O$_3$ [M+Na]$^+$: 283.1305; found: 283.1299.

1-(((5,5-Difluorohept-6-yn-1-yl)oxy)methyl)-4-methoxybenzene 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. NaHCO₃ 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 Na₂SO₄ 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; ¹H NMR (500 MHz, CDCl₃) δ = 1.62-1.78 (4H, m, CH₂), 2.02-2.11 (2H, m, CH₂), 2.76 (1H, t, J(H,F)= 4.9 Hz, CH), 3.47 (2H, t, J(H,H)= 5.5 Hz, CH₂), 3.82 (3H, s, CH₃), 4.45 (2H, s, CH₂), 6.88-6.90 (2H, m, ArH), 7.26-7.28 (2H, m, ArH); ¹³C NMR (125 MHz, CDCl₃) δ = 19.8 (CH₂, t, J(C,F)= 3.7 Hz), 29.2 (CH₂), 39.0 (CH₂, t, J(C,F)= 25.6 Hz), 55.5 (CH₃), 69.6 (CH₂), 72.8 (CH₂), 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); ¹⁹F {¹H} NMR (282 MHz, CDCl₃) δ = -84.0 (2F, s, CF₂); 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 C₁₅H₁₈F₂NaO₂ [M+Na]⁺: 291.1167; found: 291.1161.

1-(((6,6-Difluoroct-7-yn-1-yl)oxy)methyl)-4-methoxybenzene 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-difluoroct-7-yn-1-yl)oxy)methyl)-4-methoxybenzene 28b (1.93 g, 51%) as an orange oil; ¹H NMR (500 MHz, CDCl₃) δ = 1.41-1.67 (6H, m, CH₂), 1.99-2.10 (2H, m, CH₂), 2.75 (1H, t, J(H,F)= 4.9 Hz, CH), 3.46 (2H, t, J(H,H)= 6.4 Hz, CH₂), 3.46 (3H, s, CH₃), 4.44 (2H, s, CH₂), 6.87-6.91 (2H, m, ArH), 7.26-7.29 (2H, m, ArH); ¹³C NMR (125 MHz, CDCl₃) δ = 22.7 (CH₂, t, J(C,F)= 3.4 Hz), 25.8 (CH₂), 29.7 (CH₂), 39.2 (CH₂, t, J(C,F)= 25.6 Hz), 55.5 (CH₃), 69.9 (CH₂), 72.8 (CH₂), 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 (CF₂, t, J(C,F)= 233.0 Hz), 129.5 (CH), 130.8 (C), 159.3 (C); ¹⁹F {¹H} NMR (376 MHz, CDCl₃) δ = -84.5
nBuLi (1.6 M in hexanes, 3.0 mL, 4.8 mmol, 1.0 eq) was added to a solution of (((6,6-difluoroct-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 (4R)-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. NH₄Cl 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 Na₂SO₄ and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4) gave (2R)-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; [α]₀ +2.3° (c 1.02, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ = 0.96 (3H, d, J(H,H)= 6.6 Hz, CH₃), 0.97 (3H, d, J(H,H)= 6.6 Hz, CH₃), 1.29-1.38 (1H, m, CH₂-3), 1.44-1.51 (2H, m, CH₂-10), 1.58-1.86 (11H, CH-2, CH₂-3,4,11,12, OH), 2.00-2.09 (2H, m, CH₂-9), 3.30-3.36 (2H, m, CH₂-1), 3.47 (2H, t, J(H,H)= 6.3 Hz, CH₂-13), 3.83 (3H, s, CH₃), 4.39-4.45 (1H, m, CH-5), 4.45 (2H, s, CH₂), 4.52 (2H, s, CH₂), 6.89-6.92 (2H, m, ArH), 7.29-7.38 (7H, m, ArH); ¹³C NMR (125 MHz, CDCl₃) δ = 17.3 and 17.4 (CH₃), 22.8 (CH₂, t, J(C,F)= 2.9 Hz, C10), 25.8 (CH₂, C11), 29.2 and 29.2 (CH₂, C3), 29.6 (CH₂, C12), 33.3 and 33.3 (CH, C2), 34.7 and 34.8 (CH₂, C4), 39.2 (CH₂, t, J(C,F)= 26.0 Hz, C9), 55.5 (CH₃), 62.3 and 62.4 (CH, C5), 69.9 (CH₂, C13), 72.8 (CH₂, Bn), 73.2 (CH₂, PMB), 75.8 (CH₂, C1), 77.9-78.2 (C, m, C7), 88.1-88.3 (C, m, C6), 114.0 (CH), 115.0 (CF₂, 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$_3$) $\delta$ = -83.09 and -83.10 (2F, s, CF$_2$); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -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) $\nu$(cm$^{-1}$) = 3401, 2936, 2864, 2250, 1613, 1513, 1455, 1248, 1174, 1097, 739, 699; MS (ESI) 511 (100) [M+Na]$^+$, 491 (20); HRMS: m/z calcd for C$_{29}$H$_{38}$F$_2$NaO$_4$ [M+Na]$^+$: 511.2630; found: 511.2621.

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

DMP (1.46 g, 3.4 mmol, 1.5 eq) was added to a solution of (2R)-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$_2$SO$_4$ and the solvent was removed in vacuo to give (2R)-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$_3$) $\delta$ = 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$_3$) $\delta$ = 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$_3$) $\delta$ = -85.5 (2F, s, CF$_2$); $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ = -86.0 (2F, t,
$J(H,F) = 15.2 \text{ Hz, CF}_2$; MS (ESI) 509 (100) [M+Na]$^+$$^\ddagger$, 489 (20); HRMS: $m/z$ calcd for C$_{29}$H$_{36}$F$_2$Na$_4$O$_4$ [M+Na]$^+$$^\ddagger$: 509.2474; found: 509.2463.

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

DAST (1.4 mL, 10.2 mmol, 4.0 eq) was added to a Teflon flask containing (2R)-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$_2$SO$_4$ and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:9) gave 1-(((12R)-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; $[\alpha]_D +3.5^\circ$ (c 1.05, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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$_3$) $\delta$ = 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$_3$, 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$_3$) $\delta$ = -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$_3$) $\delta$ = -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) $\nu$(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]$^+$$^\ddagger$, 511 (45); HRMS: $m/z$ calcd for C$_{29}$H$_{36}$F$_4$Na$_4$O$_4$ [M+Na]$^+$$^\ddagger$: 531.2493; found: 531.2483.
(12R)-12-((Benzyloxy)methyl)-6,6,9,9-tetrafluorotridec-7-yn-1-ol 31

DDQ (0.54 g, 2.4 mmol, 1.5 eq) was added to a solution of 1-(((12R)-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. NaHCO₃ 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 Na₂SO₄ and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4) gave (12R)-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; [α]D +5.4° (c 1.02, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ = 0.97 (2H, d, J(H,H)= 6.6 Hz, CH₃), 1.38-1.50 (8H, m, CH₂-2,3,4,11, OH), 1.56-1.62 (1H, m, CH₂-11), 1.81-1.88 (1H, m, CH₂-12), 2.04-2.16 (4H, m, CH₂-5,10), 3.28-3.36 (2H, m, CH₂-13), 3.65 (2H, t, J(H,H)= 6.5 Hz, CH₂-1), 4.51 (2H, s, CH₂), 7.27-7.38 (5H, m, ArH); ¹³C NMR (125 MHz, CDCl₃) δ = 17.0 (CH₃), 22.5 (CH₂, t, J(C,F)= 3.3 Hz, C4), 25.3 (CH₂, C2), 26.5 (CH₂, t, J(C,F)= 3.3 Hz, C11), 32.5 (CH₂, C3), 33.0 (CH, C12), 36.6 (CH₂, t, J(C,F)= 25.0 Hz, C10), 38.9 (CH₂, t, J(C,F)= 25.2 Hz, C5), 62.7 (CH₂, C1), 73.3 (CH₂, Bn), 75.3 (CH₂, C13), 78.8-79.5 (C, m, C7/C8), 114.3 (CH₂, t, J(C,F)= 235.6 Hz, C6), 114.5 (CH₂, t, J(C,F)= 235.6 Hz, C9), 127.8 (CH), 127.8 (CH), 128.6 (CH), 138.6 (C); ¹⁹F {¹H} NMR (470 MHz, CDCl₃) δ = -85.4 (2F, t, J(C,F)= 4.8 Hz, CF₂), -85.6 (2F, t, J(C,F)= 4.8 Hz, CF₂); ¹⁹F NMR (470 MHz, CDCl₃) δ = -85.4 (2F, tt, J(H,F)= 15.2 Hz, J(F,F)= 4.9 Hz, CF₂), -85.6 (2F, tt, J(H,F)= 15.1 Hz, J(F,F)= 4.9 Hz, CF₂); 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 C₂₁H₂₆F₄Na₂O₂ [M+Na]⁺: 411.1918; found: 411.1918.

(12R)-12-((Benzyloxy)methyl)-6,6,9,9-tetrafluorotridec-7-ynoic acid 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 (12R)-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$_2$SO$_4$ and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4, 1% AcOH) gave (12R)-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$_3$) $\delta$ = 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$_3$), 3.35 (1H, dd, $J$(H,H) = 7.2, 5.8 Hz, CH$_3$), 4.53 (2H, s, CH$_2$), 7.27-7.38 (5H, m, ArH); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 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$_3$) $\delta$ = -85.3-(-85.3) (2F, m, CF$_2$), -85.4-(-85.4) (2F, m, CF$_2$); $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ = -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$_4$Na$_2$O$_3$ [M+Na]$^+$: 425.1710; found: 425.1702.

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

A solution of (12R)-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 (12R)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoate 33 (0.227 g, 65%) as a white solid; mp 40-42 °C; $[\alpha]_D +6.2^\circ$ (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), 32.9 (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{$_1^1$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$_{18}$H$_{30}$F$_4$Na$_4$O$_3$ [M+NH$_4$]$^+$: 348.2156; found: 348.2157.

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

Lithium hydroxide (22 mg, 0.93 mmol, 4.2 eq) was added to a solution of methyl (12R)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoate 33 (73 mg, 0.22 mmol, 1.0 eq) in THF (3 mL) and H$_2$O (3 mL) at r.t. and stirred for 3 h. The reaction mixture was quenched with sat. NH$_4$Cl 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$_2$SO$_4$ and the solvent was removed in vacuo to give (12R)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoic acid 34 (70 mg, 94%) as a white solid; mp 90-93 °C; $[\alpha]_D +12.6^\circ$ (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$_3$) $\delta$ = 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), 68.1 (CH$_2$, C13), 124.5 (CF$_2$, t, $J$(C,F)= 24.0 Hz, C6/C9), 124.7 (CF$_2$, t, $J$(C,F)= 241.4 Hz, C6/C9), 177.5 (CO); $^{19}$F{H} NMR (470 MHz, CDCl$_3$) $\delta$ = -99.85 (1F, s, CF$_2$), -78.86 (1F, s, CF$_2$), -99.2 (2F, s, CF$_2$); $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ = -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$_4$O$_3$ [M-H]$^-$: 315.1589; found: 315.1598.

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

![Structure of 8](image)

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 (12R)-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$_2$SO$_4$ and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (13R)-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$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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$_3$H$_{18}$-14), 4.21 (1H, dd, $J$(H,H)= 11.1, 3.4 Hz, CH$_3$H$_{18}$-14); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 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 (CH2, t, J(C,F) = 25.3 Hz, C6), 35.4 (CH2, C2), 67.9 (CH2, C14), 125.2 (CF2, t, J(C,F) = 240.9 Hz, C7), 125.5 (CF2, t, J(C,F) = 240.9 Hz, C10), 173.1 (CO, C2); 19F{1H} NMR (470 MHz, CDCl3) δ = -91.01 (1F, s, CF2), -91.04 (1F, s, CF2), -91.09 (1F, d, J(F,F) = 246.9 Hz, CF2A), -92.2 (1F, d, J(F,F) = 246.9 Hz, CF2B); 13C NMR (125 MHz, CDCl3) δ = 17.2 and 17.2 (CH3), 29.9 and 30.0 (CH2), 30.1 and 30.2 (CH2), 33.5 and 33.5 (CH), 47.3 and 47.4 (CH2), 52.7 and 52.7 (CH), 73.5 and 73.5 (CH), 75.8 (CH2), 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 C14H20Na1O2 [M+Na]+: 243.1356; found: 243.1350

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

mCPBA (3.45 g, 20 mmol, 2.0 eq) was added to a solution of (((2R)-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. NaHCO3 solution (200 mL), brine (200 mL), dried over anhydrous Na2SO4 and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave 2-((3R)-4-(benzyloxy)-3-methylbutyl)oxirane 13 (1.88 g, 55%) as a colourless oil as a 1:1 mixture of diastereoisomers; [α]D +3.4° (c 0.99, CHCl3); 1H NMR (500 MHz, CDCl3) δ = 0.95 (3H, d, J(H,H) = 6.7 Hz, CH3) and 0.96 (3H, d, J(H,H) = 6.8 Hz, CH3), 1.24-1.36 (1H, m, CH2), 1.49-1.69 (3H, m, CH2), 1.78-1.86 (1H, m, CH), 2.47-2.49 (1H, m, CH2), 2.74-2.77 (1H, m, CH2), 2.90-2.93 (1H, m, CH), 3.27-3.35 (2H, m, CH2), 4.51 (2H, m, CH2), 7.27-7.37 (5H, m, ArH); 13C NMR (125 MHz, CDCl3) δ = 17.2 and 17.2 (CH3), 29.9 and 30.0 (CH2), 30.1 and 30.2 (CH2), 33.5 and 33.5 (CH), 47.3 and 47.4 (CH2), 52.7 and 52.7 (CH), 73.2 and 73.2 (CH2), 75.8 (CH2), 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 C14H20Na1O2 [M+Na]+: 243.1356; found: 243.1350
(2R)-2-((Benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-yn-5-ol 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-((3R)-4-(benzyloxy)-3-methylbutyl)oxirane 13 (4.5 g, 20.3 mmol, 1.5 eq) gave (2R)-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; [α]D +1.8° (c 1.04, CHCl3); 1H NMR (500 MHz, CDCl3) δ = 0.94 (3H, d, J(H,H)= 6.7 Hz, CH3) and 0.95 (3H, d, J(H,H)= 6.7 Hz, CH3), 1.13-1.33 (1H, m, CH2-3), 1.46-1.72 (7H, m, CH2-3,4,11,12), 1.76-1.85 (1H, m, CH-2), 1.91 (1H, bs, OH), 2.00-2.08 (2H, m, CH2-10), 2.38-2.62 (2H, m, CH2-6), 3.27-3.33 (2H, m, CH2-1), 3.45-3.47 (2H, m, CH2-13), 3.74-3.79 (1H, m, CH-5), 3.81 (3H, s, CH3), 4.44 (2H, s, CH2), 4.51 (2H, s, CH2), 6.88-6.90 (2H, m, ArH), 7.26-7.37 (7H, m, ArH); 13C NMR (125 MHz, CDCl3) δ = 17.3 and 17.3 (CH3), 20.1 (CH2, C12), 27.4 and 27.6 (CH2, C6), 29.2 (CH2, C11), 29.7 and 29.7 (CH2, C3), 33.4 and 33.6 (CH, C2), 33.9 and 33.9 (CH2, C4), 39.3 (CH2, t, J(C,F)= 26.5 Hz, C10), 55.5 (CH3), 69.6 (CH2, C13), 69.9 and 70.1 (CH, C5), 72.8 (CH2, PMB), 73.2 and 73.3 (CH2, Bn), 75.8 and 75.9 (CH2, 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 (CF2, 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); 19F {1H} NMR (470 MHz, CDCl3) δ = -81.25 and -81.26 (2F, s, CF2); MS (ESI) 511 (100) [M+Na]+; HRMS: m/z calcd for C29H38F2Na4O4 [M+Na]+: 511.2630; found: 511.2620.

(2R,7Z)-2-((Benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-ol 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 (2R)-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 (2R,7Z)-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; [α]D +0.8° (c 1.02, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ = 0.95 (3H, d, J(H,H)= 6.2 Hz, CH₃) and 0.96 (3H, d, J(H,H)= 6.3 Hz, CH₃), 1.16-1.34 (1H, m, CH₂-3), 1.40-1.69 (8H, m, CH₂-3,4,11,12, OH), 1.77-1.82 (1H, m, CH-2), 1.90-2.00 (2H, m, CH₂-10), 2.38-2.50 (2H, m, CH₂-6), 3.28-3.36 (2H, m, CH₂-1), 3.47 (2H, t, J(H,H)= 6.2 Hz, CH₂-13), 3.67-3.68 (1H, m, CH-5), 3.83 (3H, s, CH₃), 4.45 (2H, s, CH₂), 4.52 (2H, s, CH₂), 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); ¹³C NMR (125 MHz, CDCl₃) δ = 17.3 and 17.4 (CH₃), 19.4 (CH₂, t, J(C,F)= 3.9 Hz, C12), 29.6 (CH₂, C11), 29.8 and 29.8 (CH₂, C3), 33.5 and 33.7 (CH, C2), 34.7 and 34.8 (CH₂, C4), 36.3 and 36.4 (CH₂, C6), 38.4 (CH₂, t, J(C,F)= 38.4 Hz, C10), 55.5 (CH₃), 69.8 (CH₂, C13), 71.7 and 71.9 (CH, C5), 72.8 (CH₂, PMB), 73.2 and 73.2 (CH₂, Bn), 75.8 and 76.0 (CH₂, C1), 114.0 (CH), 122.7 (CF₂, 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); ¹⁹F {¹H} NMR (470 MHz, CDCl₃) δ = -90.2 and -90.2 (1F, d, J(F,F)= 248.0 Hz, CF₃F₄B), -90.7 and -90.7 (1F, d, J(F,F)= 248.0 Hz, CF₃F₄B); ¹⁹F NMR (470 MHz, CDCl₃) δ = -90.2 (1F, d, J(F,F)= 248.0 Hz, CF₃F₄B), -90.7 and -90.7 (1F, d, J(F,F)= 248.0 Hz, CF₃F₄B); MS (ESI) 603 (35), 531 (65), 513 (100) [M+Na]⁺, 121 (30); HRMS: m/z calcd for C₂₉H₄₀F₂NaO₄ [M+Na]⁺: 513.2787; found: 513.2785.

(2R,7Z)-2-((Benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-one 36
Following the same procedure reported for 29, (2R,7Z)-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 (2R,7Z)-2-((benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-one 36 (0.90 g, 57%) as a colourless oil; \([\alpha]_D^0\) -0.4° (c 1.01, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta = 0.93\) (3H, d, \(J(H,H) = 6.6\) Hz, CH₃), 1.43-1.84 (7H, m, CH₂-2, CH₂-3,11,12), 1.86-1.98 (2H, m, CH₂-10), 2.20-2.63 (2H, m, CH₂-6), 3.27-3.347 (2H, m, CH₂-1), 3.42-3.47 (4H, m, CH₂-4,13), 3.81 (3H, s, CH₃), 4.44 (2H, s, CH₂), 4.49 (2H, s, CH₂), 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); \(^1^3\)C NMR (125 MHz, CDCl₃) \(\delta = 17.2\) (CH₃), 19.3 (CH₂, t, \(J(C,F) = 4.1\) Hz, C12), 27.8 (CH₂, C3), 29.5 (CH₂, C11), 33.2 (CH₂, C2), 38.2 (CH₂, t, \(J(C,F) = 26.4\) Hz, C10), 40.5 (CH₂, C6), 41.6 (CH₂, C4), 55.5 (CH₃), 69.7 (CH₂, C13), 72.8 (CH₂, PMB), 73.2 (CH₂, Bn), 75.6 (CH₂, C1), 114.0 (CH), 122.6 (CF₂, t, \(J(C,F) = 239.7\) Hz, C9), 127.1 (CH₂, t, \(J(C,F) = 26.4\) Hz, C8), 127.7 (CH), 127.8 (CH), 128.5 (CH), 129.1 (CH₂, t, \(J(C,F) = 5.4\) Hz, C7), 129.4 (CH), 130.7 (C), 138.8 (C), 159.3 (CH), 207.7 (CO, C5); \(^1^9\)F{\(^1\)H} NMR (470 MHz, CDCl₃) \(\delta = -91.8\) (-91.9) (2F, s, CF₂); MS (ESI) 511 (100) \([M+Na]^+\), 121 (40); HRMS: m/z calcd for C₂₉H₃₈F₂NaO₄ \([M+Na]^+\): 511.2630; found: 511.2627.

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

Following the same procedure reported for 30, (2R,7Z)-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-(((6Z,12R)-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; \([\alpha]_D^0\) 1.2° (c 1.53, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta = 0.95\) (3H, d, \(J(H,H) = 6.7\) Hz, CH₃), 1.30-1.70 (6H, m, CH₂-2,3,11), 1.76-1.98 (5H, CH-12, CH₂-4,10), 2.82-3.03 (2H, m, CH₂-8), 3.28-3.36 (2H, m, CH₂-13), 3.45 (2H, t, \(J(H,H) = 6.2\) Hz, CH₂-1), 3.81 (3H, s, CH₃), 4.44 (2H, s, CH₂), 4.51 (2H, s, CH₂), 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); \(^1^3\)C NMR (125 MHz, CDCl₃) \(\delta = 17.1\) (CH₃), 19.3 (CH₂, t, \(J(C,F) = 4.0\) Hz, C3), 26.0
(CH₂, t, J(C,F) = 4.1 Hz, C11), 29.6 (CH₂, C2), 33.3 (CH₂, C12), 34.1 (CH₂, t, J(C,F) = 24.9 Hz, C10), 35.7 (CH₂, t, J(C,F) = 26.1 Hz, C8), 38.3 (CH₂, t, J(C,F) = 26.5 Hz, C4), 55.5 (CH₃), 69.7 (CH₂, C1), 72.8 (CH₂, PMB), 73.2 (CH₂, Bn), 75.6 (CH₂, C13), 114.0 (CH), 122.5 (CF₂, t, J(C,F) = 239.4 Hz, C9), 124.2 (CF₂, 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), 128.6 (CH), 129.4 (CH), 130.7 (C), 138.8 (C), 159.4 (C); ¹⁹F {¹H} NMR (470 MHz, CDCl₃) δ = -91.8 (2F, s, CF₂), -98.5 (2F, s, CF₂); ¹⁹F NMR (470 MHz, CDCl₃) δ = -91.8 (2F, dt, J(H,F) = 15.6, 15.6 Hz, CF₂), -98.5 (2F, tt, J(H,F) = 16.5, 16.2 Hz, CF₂); MS (ESI) 632 (15), 533 (50) [M+Na]+, 121 (100); HRMS: m/z calcd for C₂₉H₃₈F₄NaO₃ [M+Na]+: 533.2649; found: 533.2642.

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

Following the same procedure reported for 31, 1-((((6Z,12R)-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 (6Z,12R)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-en-1-ol 38 (0.15 g, 70%) as a colourless oil; [α]D = -1.9° (c 1.14, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ = 0.95 (3H, d, J(H,H) = 6.7 Hz, CH₃), 13.0-1.44 (1H, m, CH₂-11), 1.54-1.70 (5H, m, CH₂-2,3,11), 1.73-2.00 (5H, CH-12, CH₂-4,10), 2.82-3.02 (2H, m, CH₂-8), 3.28-3.37 (2H, m, CH₂-13), 4.50 (2H, s, CH₂), 5.64-5.72 (1H, m, CH-6), 5.80-5.85 (1H, m, CH-7), 7.26-7.38 (5H, m, ArH); ¹³C NMR (125 MHz, CDCl₃) δ = 17.1 (CH₃), 18.8 (CH₂, t, J(C,F) = 4.1 Hz, C3), 26.1 (CH₂, t, J(C,F) = 4.0 Hz, C11), 32.4 (CH₂, C2), 33.4 (CH₂, C12), 34.2 (CH₂, t, J(C,F) = 25.0 Hz, C10), 35.7 (CH₂, t, J(C,F) = 26.3 Hz, C8), 38.3 (CH₂, t, J(C,F) = 26.5 Hz, C4), 62.6 (CH₂, C1), 73.3 (CH₂, Bn), 75.6 (CH₂, C13), 122.3 (CF₂, t, J(C,F) = 240.1 Hz, C9), 124.2 (CF₂, 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); ¹⁹F {¹H} NMR (470 MHz, CDCl₃) δ = -91.8 (1F, s, CF₂), -98.6 (1F, s, CF₂); ¹⁹F NMR (470 MHz, CDCl₃) δ = -91.8 (2F, dt, J(H,F) = 15.7, 15.4 Hz, CF₂), -98.5 (2F, tt, J(H,F) = 16.6, 16.4 Hz, CF₂); MS (ESI) 413 (100) [M+Na]+; HRMS: m/z calcd for C₂₁H₃₈F₄NaO₃ [M+Na]+: 413.2074; found: 413.2067.

(6Z,12R)-13-(Benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-enoic acid 39
Following the same procedure reported for 32, (6Z,12R)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-en-1-ol 38 (0.15 g, 0.4 mmol, 1.0 eq) gave (6Z,12R)-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$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 0.95 (3H, d, $J$(H,H)= 6.7 Hz, CH$_3$), 1.30-1.39 (1H, m, CH$_A$H$_B$-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$_3$) $\delta$ = 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{$_1$H} NMR (470 MHz, CDCl$_3$) $\delta$ = -92.0 (2F, s, CF$_2$-C5), -98.4 (2F, s, CF$_2$-C9); $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ = -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$_4$NaO$_3$ [M+Na]$^+$: 427.1867; found: 427.1861.

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

Following the same procedure reported for 33, (6Z,12R)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-enoic acid 39 (75 mg, 0.19 mmol, 1.0 eq) gave methyl (12R)-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$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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$_3$) $\delta$ = 15.5-15.7 (CH$_3$, m, C7), 16.6 (CH$_3$), 18.0
(CH₂, t, J(C,F)= 4.7 Hz, C3), 25.8 (CH₂, t, J(C,F)= 4.2 Hz, C11), 33.5 (CH₂, C2), 34.1 (CH₂, t, J(C,F)= 25.5 Hz, C10), 36.0 (CH₂, t, J(C,F)= 25.5 Hz, C4/C6), 36.1 (CH₂, t, J(C,F)= 25.5 Hz, C4/C6), 51.9 (CH₃), 68.0 (CH₂, C13), 124.8 (CF₂, t, J(C,F)= 240.7 Hz, C5/C9), 125.2 (CF₂, t, J(C,F)= 240.7 Hz, C5/C9), 173.7 (CO, C1); ¹⁹F{¹H} NMR (470 MHz, CDCl₃) δ = -98.5 (2F, s, CF₂), -98.6 (2F, s, CF₂); ¹⁹F NMR (470 MHz, CDCl₃) δ = -98.5 (2F, tt, J(H,F)= 16.5, 16.5 Hz, CF₂), -98.6 (2F, tt, J(H,F)= 16.3, 16.3 Hz, CF₂); MS (ESI) 353 (100) [M+Na]+, 316 (15); HRMS: m/z calcd for C₁₅H₂₆F₄Na₃O₃ [M+Na]+: 353.1710; found: 353.1699.

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

Lithium hydroxide (11 mg, 0.46 mmol, 4.2 eq) was added to a solution of methyl (12R)-5,5,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoate 40 (36 mg, 0.11 mmol, 1.0 eq) in THF (1 mL) and H₂O (1 mL) at r.t. and stirred for 3 h. The reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated and washed with brine (20 mL), dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo to give (12R)-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 (12R)-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. NaHCO₃ solution (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (13R)-6,6,10,10-tetrafluoro-13-methyl-1-oxacyclotetradecan-2-one 9 (12 mg, 52%) as a colourless oil; [α]D +9.2° (c 0.59, CHCl₃); ¹H NMR (500 MHz, CDCl₃)
MHz, CDCl$_3$) $\delta = 1.00$ (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$_2$-14), 4.20 (1H, dd, $J$(H,H)= 11.3, 3.4 Hz, CH$_2$-14);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta =$ 16.9 (CH$_3$), 17.9 (CH$_2$), 19.0 (CH$_2$, t, $J$(C,F)= 5.5 Hz, C8), 25.8 (CH$_2$, t, $J$(C,F)= 5.5 Hz, C4), 31.8 (CH, C13), 33.8 (CH$_2$, t, $J$(C,F)= 5.5 Hz, C8), 34.3 (CH$_2$, t, $J$(C,F)= 25.9 Hz), 34.3 (CH$_2$, t, $J$(C,F)= 240.4 Hz, C6), 125.6 (CF$_2$, t, $J$(C,F)= 240.4 Hz, C10), 172.7 (CO, C2);

$^{19}$F NMR (470 MHz, CDCl$_3$) $\delta =$ -91.0 (2F, s, CF$_2$), -91.2 (1F, d, $J$(F,F)= 248.5 Hz, CF$_A$F$_B$), -91.8 (1F, s, CF$_A$F$_B$);

HRMS: m/z calcd for C$_{14}$H$_{26}$F$_4$N$_1$O$_2$ [M+NH$_4^+$]: 316.1894; found: 316.1888.

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

![BnO](image)

9-BBN dimer (3.66 g, 15 mmol, 1.0 eq) was added to a solution of (2R)-2-methylhex-5-en-1-ol (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$_2$SO$_4$ and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4) gave (5R)-6-(benzyloxy)-5-methylhexan-1-ol 50 (1.99 g, 59%) as a colourless oil; [$\alpha$]$_D^0$ +0.7° (c 1.05, CHCl$_3$); $^1$H NMR (500 MHz, CDC$_3$) $\delta = 0.94$ (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$_A$H$_B$), 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$_A$H$_B$), 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$_3$) $\delta =$ 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$_1$O$_2$ [M+Na]$^+$: 245.1512; found: 245.1509.

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

DMP (4.53 g, 10.7 mmol, 1.2 eq) was added to a solution of (5R)-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$_2$SO$_4$ and the solvent was removed in vacuo to give (5R)-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$_3$) $\delta = 0.95$ (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$_{3}$H$_6$), 3.32 (1H, dd, $J$(H,H)= 9.1, 6.3 Hz, CH$_{3}$H$_6$), 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$_3$) $\delta = 17.2$ (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

6-Heptyl-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$_2$SO$_4$ 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$_3$) $\delta =$ 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$_3$) $\delta =$ 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) $\nu$ (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$_{20}$NaO$_2$ [M+Na]$^+$: 255.1356; found: 255.1350.

(2R)-2-((Benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-ol 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 (5R)-6-(benzyloxy)-5-methylhexanal 14 (1.96 g, 8.9 mmol, 1.1 eq) gave (2R)-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$^\circ$ (c 1.07, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta =$ 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$_A$H$_B$-1), 3.31-3.35 (1H, m, CH$_A$H$_B$-1), 3.44 (2H, s, CH$_2$), 4.49 (1H, d, $J$(H,H)= 12.5 Hz, CH$_A$H$_B$), 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$_3$) $\delta =$ 17.3 and 17.3 (CH$_3$), 18.9 (CH$_2$), 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) $\nu$ (cm$^{-1}$) = 3413, 2935, 2862, 2212, 1613, 1513, 1454, 1248, 1097,
Following the same procedure reported for 29, (2R)-2-((benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-one 44 (1.72 g, 61%) as a colourless oil; [α]D +0.2° (c 1.03, CHCl3); 1H NMR (500 MHz, CDCl3) δ = 0.95 (3H, d, J(H,H)= 6.7 Hz, CH3), 1.11-1.19 (1H, m, CH2-3), 1.43-1.81 (11H, m, CH-2, CH2-3,4,10,11,12), 2.36 (2H, t, J(H,H)= 7.1 Hz, CH2-9), 2.47-2.57 (2H, m, CH2-5), 3.26 (1H, dd, J(H,H)= 8.9, 6.4 Hz, CHAHB-1), 3.32 (1H, dd, J(H,H) = 9.1, 6.2 Hz, CHAHB-1), 3.45 (2H, t, J(H,H)= 6.7 Hz, CH2-13), 3.81 (3H, s, CH3), 4.43 (2H, s, CH2), 4.49 (1H, d, J(H,H)= 12.6 Hz, CHAHB), 4.51 (1H, d, J(H,H)= 12.6 Hz, CHAHB), 6.87-6.89 (2H, m, ArH), 7.26-7.37 (7H, m, ArH); 13C NMR (125 MHz, CDCl3) δ = 17.2 (CH3), 19.1 (CH2, C9), 21.8 (CH2, C4), 25.8 (CH2, C11), 27.8 (CH2, C10), 29.4 (CH2, C12), 33.1 (CH2, C3), 33.6 (CH, C2), 46.0 (CH2, C5), 55.5 (CH3), 69.9 (CH2, C13), 72.8 (CH2, PMB), 73.2 (CH2, Bn), 75.9 (CH2, 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 C29H38Na1O4 [M+Na]+: 473.2662; found: 473.2650.

Following the same procedure reported for 30, (2R)-2-((benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-one 44 (1.7 g, 3.8 mmol, 1.0 eq) gave 1-(((12R)-13-(Benzyloxy)-8,8-difluoro-12-methyltridec-6-yn-1-ol)oxy)methyl)-4-methoxybenzene 45
(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$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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$_A$H$_B$-1), 3.32 (1H, dd, $J$(H,H)= 9.0, 6.3 Hz, CH$_A$H$_B$-1), 3.45 (2H, t, $J$(C,F)= 26.7 Hz, CH$_5$), 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$_3$) $\delta$ = 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 NMR (376 MHz, CDCl$_3$) $\delta$ = -81.1 (1F, d, $J$(F,F)= 267.0 Hz, CF$_A$F$_B$), -81.9 (1F, d, $J$(F,F)= 267.0 Hz, CF$_A$F$_B$); $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ = -80.7 (1F, dm, $J$(F,F)= 267.3 Hz, CF$_A$F$_B$), -81.3 (1F, dm, $J$(F,F)= 267.3 Hz, CF$_A$F$_B$); IR (thin film) $\nu$ (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$_2$Na$_1$O$_3$[M+Na]$^+$: 495.2681; found: 495.2671.

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$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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$_3$) $\delta$ = 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, C1), 88.5 (C, t, J(C,F)= 6.5 Hz, C8), 115.2 (CF2, t, J(C,F)= 230.7 Hz, C6), 127.7 (CH), 127.8 (CH), 128.6 (CH), 138.8 (C); 19F{1H} NMR (376 MHz, CDCl3) δ = -81.1 (1F, d, J(F,F)= 267.4 Hz, CF3F), -81.9 (1F, d, J(F,F)= 267.4 Hz, CF3F); 19F NMR (376 MHz, CDCl3) δ = -81.1 (1F, dm, J(F,F)= 267.1 Hz, CF2), -81.9 (1F, dm, J(F,F)= 267.1 Hz, CF2); 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 C21H30F2NaO2 [M+Na]+: 375.2106; found: 375.2096.

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

Following the same procedure reported for 32, (12R)-13-(benzyloxy)-8,8-difluoro-12-methyltridec-6-yn-1-ol 46 (280 mg, 0.8 mmol, 1.0 eq) gave (12R)-13-(benzyloxy)-8,8-difluoro-12-methyltridec-6-ynoic acid 47 (0.14 g, 48%) as a yellow oil; [α]D +1.0° (c 0.64, CHCl3); 1H NMR (500 MHz, CDCl3) δ = 0.94 (3H, d, J(H,H)= 6.7 Hz, CH3), 1.15-1.25 (1H, m, CH2-3), 1.48-1.65 (5H, m, CH2-3,4,10), 1.73-1.82 (3H, m, CH-2, CH2-11), 1.95-2.04 (2H, m, CH2-5), 2.29-2.33 (2H, m, CH2-9), 2.39 (2H, t, J(H,H)= 7.3 Hz, CH2-12), 3.27-3.33 (2H, m, CH2-1), 4.52 (2H, s, CH2), 7.27-7.37 (5H, m, ArH); 13C NMR (125 MHz, CDCl3) δ = 17.1 (CH3), 18.3 (CH2, C9), 20.7 (CH2, C4), 24.0 (CH2, C11), 27.3 (CH2, C10), 33.2 (CH2, C3), 33.4 (CH2, C12), 33.6 (CH, C2), 39.9 (CH2, t, J(C,F)= 26.4 Hz, C5), 73.2 (CH2, Bn), 74.7 (C, t, J(C,F)= 40.4 Hz, C7), 75.9 (CH, C2, C1), 87.9 (C, t, J(C,F)= 6.8 Hz, C8), 115.2 (CF2, t, J(C,F)= 231.2 Hz, C6), 127.7 (CH), 127.8 (CH), 128.6 (CH), 138.6 (C); 19F{1H} NMR (470 MHz, CDCl3) δ = -80.8 (1F, d, J(F,F)= 267.2 Hz, CF2), -81.6 (1F, d, J(F,F)= 267.2 Hz, CF2); 19F NMR (376 MHz, CDCl3) δ = -81.3 (1F, dtt, J(F,F)= 267.7 Hz, J(H,F)= 14.4, 5.0 Hz, CF2); -82.1 (1F, dtt, J(F,F)= 267.7 Hz, J(H,F)= 15.0, 5.0 Hz, CF2); MS (ESI) 365 (100) [M-H]-, 345 (30); HRMS: m/z calcd for C21H30F2O3 [M-H]−: 365.1934; found: 365.1929.

(12R)-8,8-Difluoro-13-hydroxy-12-methyltridecanoic acid 48
A solution of (12R)-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 (12R)-8,8-difluoro-13-hydroxy-12-methyltridecanoic acid 48 (42 mg, 46%) as a white solid; mp 67-68 °C; [α]D +8.0° (c 0.23, MeOH); 1H NMR (500 MHz, CDCl3) δ = 0.94 (3H, d, J(H,H)= 6.7 Hz, CH3), 1.12-1.22 (1H, m, CH2-11), 1.36-1.69 (13H, m, CH2-3,4,5,6,10,11, CH-12), 1.76-1.85 (4H, m, CH2-7,9), 2.36 (2H, t, J(H,H)= 7.4 Hz, CH2-2), 3.47 (1H, dd, J(H,H)= 10.5, 6.2 Hz, CHAHB-1), 3.52 (1H, dd, J(H,H)= 10.5, 6.0 Hz, CHAHB-1); 13C NMR (125 MHz, CDCl3) δ = 16.6 (CH3), 20.0 (CH2, t, J(C,F)= 4.5 Hz, C10), 22.3 (CH2, t, J(C,F)= 4.5 Hz, C6), 24.6 (CH2, C3), 28.9 (CH2, C4/C5), 29.1 (CH2, C4/C5), 33.0 (CH2, C11), 34.0 (CH2, C2), 35.7 (CH, C12), 36.4 (CH2, t, J(C,F)= 25.5 Hz, C9), 36.7 (CH2, t, J(C,F)= 25.5 Hz, C7), 68.3 (CH2, C13), 125.5 (CF2, t, J(C,F)= 239.2 Hz, C8), 179.3 (CO2H, C1); 19F {1H} NMR (470 MHz, CDCl3) δ = -97.7 (2F, s); 19F NMR (470 MHz, CDCl3) δ = -97.7 (2F, tt, J(H,F)= 16.6, 16.5 Hz, CF2); MS (ESI) 559 (15) [2M-H]−, 279 (100) [M-H]−; HRMS: m/z calcd for C14H25F2O3 [M-H]−: 279.1777; found: 279.1773.

(13R)-9,9-Difluoro-13-methyl-1-oxacyclotetradecan-2-one 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 (12R)-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. NaHCO₃ solution (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (13R)-9,9-difluoro-13-methyl-1-oxacyclotetradecan-2-one 10 (24 mg, 67%) as a white solid; mp 51-53 °C; [α]D +5.9° (c 0.59, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ = 0.97 (3H, d, J(H,H)= 7.0 Hz, CH₃), 1.32-1.52 (10H, m, CH₂-5,6,7,11,12), 1.63-1.71 (2H, m, CH₂-4), 1.76-1.99 (5H, m, CH-13, CH₂-8,10), 2.33-2.45 (2H, m, CH₂-3), 3.80 (1H, dd, J(H,H)= 11.2, 7.4 Hz, CH₃H₅B-14), 4.13 (1H, dd, J(H,H)= 11.2, 3.9 Hz, CH₃H₅B-14); ¹³C NMR (125 MHz, CDCl₃) δ = 17.7 (CH₃), 19.9 (CH₂, t, J(C,F)= 5.3 Hz, C7/C11), 20.2 (CH₂, t, J(C,F)= 4.8 Hz, C7/C11), 24.3 (CH₂, C4), 26.1 (CH₂, C5), 26.5 (CH₂, C6), 31.6 (CH, C13), 32.4 (CH₂, t, J(C,F)= 25.7 Hz, C8/C10), 32.6 (CH₂, C12), 35.0 (CH₂, C3), 35.1 (CH₂, t, J(C,F)= 25.0 Hz, C8/C10), 68.0 (CH₂, C14), 126.7 (CF₂, J(C,F)= 240.4 Hz, C9), 174.0 (CO, C2); ¹⁹F{¹H} NMR (470 MHz, CDCl₃) δ = -90.4 (1F, d, J(F,F)= 243.5 Hz, CF₆F₅) -91.0 (1F, d, J(F,F)= 243.5 Hz, CF₆F₅); ¹⁹F NMR (470 MHz, CDCl₃) δ = -90.4 (1F, dm, J(F,F)= 243.5 Hz, CF₆F₅), -91.0 (1F, dm, J(F,F)= 243.5 Hz, CF₆F₅); HRMS: m/z calcld for C₁₄H₂₈F₂N₄O₃ [M+NH₄]+: 280.2083; found: 280.2086

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

Synthesis of Moshers derivative 55. Reagents and conditions: a) (i) 2-Oxazolidinone 51, nBuLi, THF, -78 °C, 30 min. (ii) Pivaloyl chloride, NEt₃, THF, 0 °C, 30 min, r.t., 1.5 h, 50%; b) NaHMDS, MeI, THF, -78 °C, 3 h, 34%; c) LiAlH₄, Et₂O, 0 °C, 2 h, 24%; d) (R)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride, NEt₃, 4-DMAP, DCM, r.t., 18 h, 78%.
nBuLi (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. NH₄Cl solution (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with sat. NaHCO₃ solution (50 mL), sat. NH₄Cl solution (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄ 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; ¹H NMR (500 MHz, CDCl₃) δ = 1.78 (2H, tt, J(H,H)= 7.5, 7.4 Hz, CH₂), 1.78 (2H, tt, J(H,H)= 7.4, 7.2 Hz, CH₂), 2.12-2.16 (2H, m, CH₂), 2.93 (2H, t, J(H,H)= 7.5 Hz, CH₂), 2.94 (2H, t, J(H,H)= 7.4 Hz, CH₂), 4.00-4.04 (2H, m, CH₂), 4.40-4.44 (2H, m, CH₂), 4.98-5.07 (2H, m, CH₂), 5.77-5.85 (1H, m, CH); ¹³C NMR (125 MHz, CDCl₃) δ = 23.6 (CH₂), 33.2 (CH₂), 34.6 (CH₂), 42.7 (CH₂), 62.2 (CH₂), 115.5 (CH₂), 138.0 (CH), 153.7 (CO), 173.6 (CO); MS (ESI) 206 (100) [M+Na]⁺; HRMS: m/z calcd for C₉H₁₃N₁Na₁O₃ [M+Na]⁺: 206.0788; found: 206.0781.

3-(2-Methylhex-5-enoyl)-1,3-oxazolidin-2-one 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. NH₄Cl solution (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with sat. NaHCO₃ solution (50 mL), sat. NH₄Cl solution (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄ 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; 

\[^1\text{H}\text{ NMR (500 MHz, CDCl}_3\text{) }\delta = 1.18 (3\text{H, d, } J(\text{H,H})= 6.8 \text{ Hz, CH}_3), 1.47-1.54 (1\text{H, m, CH}_A\text{H}_B), 1.83-1.90 (1\text{H, m, CH}_A\text{H}_B), 2.05-2.13 (2\text{H, m, CH}_2), 3.76 (1\text{H, tq, } J(\text{H,H})= 6.9, 6.8 \text{ Hz, CH}), 4.00-4.04 (2\text{H, m, CH}_2), 4.39-4.42 (2\text{H, m, CH}_2), 4.94-5.03 (2\text{H, m, CH}_2), 5.75-5.83 (1\text{H, m, CH}); \]^13\text{C NMR (125 MHz, CDCl}_3\text{) }\delta = 17.3 (\text{CH}_3), 31.6 (\text{CH}_2), 32.8 (\text{CH}_2), 37.1 (\text{CH}), 43.0 (\text{CH}_2), 62.0 (\text{CH}_2), 115.1 (\text{CH}_2), 138.3 (\text{CH}), 153.4 (\text{CO}), 177.5 (\text{CO}); \text{MS (ESI) 220 (100) [M+Na]^{+}); HRMS: } m/z \text{ calecd for C}_{10}\text{H}_{15}\text{N}_1\text{Na}_1\text{O}_3 \text{[M+Na]^{+}: 220.0944; found: 220.0938.}

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

\[
\text{HO} \quad \text{Me} \quad \equiv
\]

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 (2R)-2-methylhex-5-en-1-ol 23.

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

\[
\text{MeO} \quad \text{CF}_3 \quad \text{Me} \quad \equiv
\]

(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 (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 55 (23 mg, 78%) as a colourless oil, as a 1:1 mixture of diastereoisomers; 1H NMR (500 MHz, CDCl3) δ = 0.94 (3H, d, J(H,H) = 6.7 Hz, CH3, (R,S)-55), 0.95 (3H, d, J(H,H) = 6.7 Hz, CH3, (R,R)-55), 1.21-1.31 (1H, m, CHAHB), 1.42-1.51 (1H, m, CHAHB), 1.85-1.94 (1H, m, CH), 1.98-2.15 (2H, m, CH2), 3.56 (3H, bq, J(H,F) = 1.0 Hz, CH2), 4.11 (1H, dd, J(H,H) = 10.8, 6.5 Hz, CHAHB, (R,S)-55), 4.16 (1H, dd, J(H,H) = 10.8, 5.8 Hz, CHAHB, (R,R)-55), 4.20 (1H, dd, J(H,H) = 10.8, 6.5 Hz, CHAHB, (R,S)-55), 4.25 (1H, dd, J(H,H) = 10.8, 5.6 Hz, CHAHB, (R,R)-55), 4.95-5.03 (2H, m, CH2), 5.71-5.80 (1H, m, CH); 13C NMR (125 MHz, CDCl3) δ = 16.8 and 16.8 (CH3), 31.1 (CH2), 32.0 and 32.0 (CH2), 32.3 and 32.4 (CH), 55.6 (CH3), 71.2 and 71.2 (CH2), 115.0 (CH2), 123.6 (q, J(C,F) = 287.9 Hz, CF3), 127.6 (CH), 128.6 (CH x 2), 129.8 (CH), 132.5 (C), 138.4 (C), 166.9 (CO); 19F{1H} NMR (470 MHz, CDCl3) δ = -71.54 (3F, s, CF3, (R,S)-55), -71.56 (3F, s, CF3, (R,R)-55); MS (ESI) 683 (15) [2M+Na]+, 353 (100) [M+Na]+; HRMS: m/z calcld for C17H21F3NaO3 [M+Na]+: 353.1335; found: 353.1331.

(2R)-2-Methylhex-5-en-1-yl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 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 (2R)-2-Methylhex-5-en-1-yl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 56 (14 mg, 49%) as a colourless oil; 1H NMR (500 MHz, CDCl3) δ = 0.95 (3H, d, J(H,H) = 6.8 Hz, CH3), 1.20-1.30 (1H, m, CHAHB), 1.41-1.50 (1H, m, CHAHB), 1.83-1.95 (1H, m, CH), 1.98-2.15 (2H, m, CH2), 3.56 (3H, q, J(C,F) = 1.1 Hz, CH3), 4.16 (1H, dd, J(H,H) = 10.7, 5.8 Hz, CHAHB), 4.20 (1H, dd, J(H,H) = 10.7, 6.3 Hz, CHAHB), 4.94-5.03 (2H, m, CH2), 5.70-5.80 (1H, m, CH), 7.40-7.43 (3H, m, ArH), 7.52-7.54 (2H, m, ArH); 13C NMR (125 MHz, CDCl3) δ = 16.8 (CH3), 31.1 (CH2), 32.0 (CH2),
32.3 (CH), 55.6 (CH₃), 71.2 (CH₂), 115.0 (CH₂), 123.6 (q, J(C,F)= 287.3 Hz, CF₃), 127.5 (CH), 128.6 (CH x 2), 129.8 (CH), 132.5 (C), 138.4 (C), 166.9 (CO); ¹⁹F{¹H} NMR (470 MHz, CDCl₃) δ = -71.56 (3F, s, CF₃, (R,R)-56); MS (ESI) 683 (10) [2M+Na]⁺, 353 (100) [M+Na]⁺; HRMS: m/z calcd for C₁₇H₂₁F₃Na₂O₃ [M+Na]⁺: 353.1335; found: 353.1331.

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.

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<td>Conformer 8-14 (0.00)</td>
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Continuation of Table S1:
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.
Continuation of Table S2:

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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.
Continuation of Table S3:

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