Towards 20,20-difluorinated bryostatin: synthesis and biological evaluation of C17,C27-fragments

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Supplementary data

Experimental procedures not included in the main text

General experimental details

Flash column chromatography was performed using Merck silica gel (60H, 230-300 mesh). Base washed silica was prepared by stirring silica in saturated aqueous potassium hydrogen carbonate for 24 h then rinsing with deionised water until the washings were pH 7, followed by rigorous drying in an oven.

Light petroleum refers to the fraction boiling between 40 and 60 °C and was redistilled. Tetrahydrofuran was dried over sodium-benzophenone and was distilled under nitrogen. Dichloromethane was dried over CaH_2 and was distilled. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Mass spectra used electron impact ionisation (EI^+), chemical ionisation using ammonia (CI^+), electrospray ionisation in the positive mode (ES^+), atmospheric pressure chemical ionisation in the positive mode ($APCI^+$) and time of flight MS with electrospray ionisation (TOF ES^+). Low resolution mass spectra were recorded on a Waters SQD2 or on an Agilent 5975C Triple axis spectrometer. High resolution mass spectra were recorded using a Thermo Finnigan MAT95XP or on a Waters QTOF spectrometer. Infra-red spectra were measured using a Bruker Alpha P FTIR spectrometer on NaBr plates, either neat or as evaporated films. Nuclear magnetic resonance spectra were recorded using Bruker Avance 300, Bruker Ultrashield 400 or on Bruker Ultrashield 500 spectrometers at *ca.* 25 °C unless otherwise stated. Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts are relative to tetramethylsilane. Residual non-deuteriated solvent was used as the internal standard.

3-(Benzothiazol-2-ylsulfanyl)-2,2-dimethylpropanal (8). Triphenylphosphine (18 g, 68 mmol) and 2-mercaptobenzothiazole (11.4 g, 68 mmol) was added to neopentyl glycol (10 g, 96 mmol) in THF (150 mL) and the solution cooled to 0 °C. Di-isopropyl azodicarboxylate (13.4 mL) in THF (200 mL) was added dropwise over 1 h and the solution stirred at 0 °C for 2 h and at rt for 16 h. Water (200 mL) was added followed by EtOAc (200 mL) and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic extracts were washed with aqueous NaOH (1 M, 100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:EtOAc) gave 3-(benzothiazol-2-ylsulfanyl)-2,2-dimethylpropanol (14.5 g, 84 %) as a colourless oil, R_f = 0.8 (EtOAc) (Found: Found: M^+ + H, 254.0667. $C_{12}H_{16}NOS_2$ requires M, 254.0668); δ_H (400 MHz, $CDCl_3$) 0.99 (6 H, s, 2 × 2-CH_3), 3.27 and 3.31 (each 2 H, s, 1-H_2 or 3-H_2), 5.10 (1 H, br. s, OH), 7.23 (1 H, td, *J* 8.0, 1.6, ArH), 7.35 (1 H, td, *J* 7.6, 1.6, ArH) and 7.66 and 7.73 (each 1 H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 24.2, 37.5, 42.1, 67.8, 120.9, 121.0, 124.6, 126.3, 134.8, 152.0 and 169.9; *m/z* (ES^+) 276 (M^+ + 23, 100%) and 254 (M^+ + 1, 32).

Dess-Martin periodinone (2.5 g, 5.9 mmol) was added to this alcohol (1.0 g, 3.95 mmol) in DCM (20 mL) and the mixture was stirred at rt for 16 h. Saturated aqueous sodium bisulfite (15 mL) and saturated sodium bicarbonate (15 mL) were added and the mixture stirred until gas evolution stopped. The aqueous layer was extracted with DCM (3 × 20 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (75:25 light petroleum:EtOAc) gave the *title compound* **8** (0.8 g, 81 %) as a yellow oil, R_f = 0.9 (EtOAc) (Found: M^+ + H, 252.0516. $C_{12}H_{14}NOS_2$ requires M, 252.0512); ν_{max}/cm^{-1} 2976, 1774, 1726, 1460, 1428, 1241, 1095, 1017 and 757; δ_H (400 MHz, $CDCl_3$) 1.18 (6 H, s, 2 × 2-CH_3), 3.58 (2 H, s, 3-H_2), 7.22 and 7.33 (each 1 H, t, *J* 8.0, ArH), 7.67 and 7.78 (each 1 H, d, *J* 8.0, ArH) and 9.57 (1 H, s, 1-H); δ_C (100 MHz, $CDCl_3$) 21.3, 31.0, 39.1, 121.1, 121.4, 124.4, 126.1, 135.3, 152.8, 166.7 and 203.7; *m/z* (ES^+) 274 (M^+ + 23, 100%) and 252 (M^+ + 1, 52).

3-(Benzyloxymethyloxy)-2,2-dimethylpropanal (9). Di-isopropylethylamine (3.9 mL, 22 mmol) and chloromethyl benzyl ether (2.0 mL, 14 mmol) were added to neopentyl glycol (3.0 g, 29 mmol) in DCM (30 mL) and the solution was stirred at rt for 16 h. Water (20 mL) was added and the aqueous layer was extracted with DCM (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (75:25 light petroleum:EtOAc) gave 3-benzyloxymethoxy-2,2-dimethylpropanol (2.5 g, 81 %) as a colourless oil, R_f = 0.35 (65:35 light petroleum:EtOAc) (Found: M^+ + Na, 247.1306. $C_{13}H_{20}O_3Na$ requires M, 247.1305); ν_{max}/cm^{-1} 3367, 3029, 2879, 1578, 1496, 1457, 1308, 1207, 1041, 1023, 908 and 735; δ_H (400 MHz, $CDCl_3$) 0.95 (6 H, s, 2 × 2-CH_3), 3.45 and 3.47 (each 2 H, s, 1-H_2 or 3-H_2), 4.62 (2 H, s, $PhCH_2$), 4.76 (2 H, s, OCH_2O) and 7.34-7.37 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 21.9, 36.1, 69.6, 71.1, 76.5, 91.6, 127.8, 128.5 and 137.6; *m/z* (ES^+) 247 (M^+ + 23, 100%).

Molecular sieves (7.0 g), NMO (1.65 g, 14 mmol) and TPAP (82 mg, 0.23 mmol) were added to this alcohol (2.1 g, 9.4 mmol) in DCM (20 mL) and acetonitrile (5 mL) and the mixture stirred at rt for 2 h and then filtered through a pad of silica that was washed with DCM (3 × 30 mL) and EtOAc (3 × 30 mL). The filtrate and washings were concentrated under reduced

pressure and chromatography of the residue the gave *title compound* **9** (1.52 g, 73 %) as a colourless oil, R_f = 0.6 (65:35 light petroleum:EtOAc); ν_{max}/cm^{-1} 3032**,** 2936, 2877, 1703, 1474, 1455, 1157, 1109, 1044 and 738; δ_H (400 MHz, $CDCl_3$) 1.12 (6 H, s, 2 × CH_3), 3.61 (2 H, s, 3-H_2), 4.58 (2 H, s, $PhCH_2$), 4.74 (2 H, s, OCH_2O), 7.31-7.36 (5 H, m, ArH) and 9.56 (1 H, s, 1-H); δ_C (100 MHz, $CDCl_3$) 19.0, 46.8, 69.5, 72.7, 94.8, 127.8, 127.9, 128.4, 137.6 and 205.0; *m/z* (ES^+) 245 (M^+ + 23, 100%).

Ethyl 5-(2-benzothiazolylsulfanyl)-2,2-difluoro-3-hydroxy-4,4-dimethylpentanoate (12). Acid washed zinc powder (0.9 g, 14 mmol) and copper(I) chloride (cat.) were added to THF (10 mL) under nitrogen and the suspension stirred at rt for 30 min. Ethyl bromodifluoroacetate **11** (1.3 mL, 10 mmol) was added followed, after 10 min, by 3-(2-benzothiazolyl)sulfanyl-2,2-dimethylpropanal **8** (1.7 g, 6.8 mmol) in THF (5 mL). The mixture was stirred under reflux for 16 h then cooled to rt and diluted with EtOAc (20 mL). The black suspension was filtered through a plug of silica that was washed with ether (4 × 40 mL). The filtrate was concentrated under reduced pressure and chromatography of the residue (80:20 light petroleum:ether) gave the *title compound* **12** (2.11 g, 83%) as a yellow oil, R_f = 0.55 (70:30 light petroleum:EtOAc) (Found: M^+ + H, 376.0843. $C_{16}H_{20}NO_3F_2S_2$ requires M, 376.0848); ν_{max}/cm^{-1} 3182, 2956, 1775, 1459, 1428, 1307, 1074, 1004 and 756; δ_H (400 MHz, $CDCl_3$) 0.97 (3 H, t, *J* 8.8, OCH_2CH_3), 1.15 (3 H, d, *J* 5.2, 4-CH_3), 1.23 (3 H, d, *J* 2.8, 4-CH_3), 2.69 and 3.91 (each 1 H, d, *J* 14.4, 5-H), 4.03 (1 H, t, *J* 6.0, 3-H), 4.20-4.06 (2 H, m, OCH_2), 6.66 (1 H, br. d, *J* 8.0, OH), 7.25 and 7.33 (each 1 H, td, *J* 7.5, 1.1, ArH) and 7.68-7.63 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.7, 18.8, 19.5, 36.1, 46.4, 62.5, 71.4 (t, $^2J_{C\text{-}F}$ 22), 117.5 (t, $^1J_{C\text{-}F}$ 251), 120.5, 121.2, 124.9, 126.5, 134.7, 151.6, 164.1 (t, $^2J_{C\text{-}F}$ 30) and 170.4; δ_F (376 MHz, $CDCl_3$) −122.42 and −103.68 (each d, $^2J_{F\text{-}F}$ 246.7); *m/z* (ES^+) 398 (M^+ + 23, 52%) and 376 (M^+ + 1, 100).

Ethyl 5-benzyloxymethoxy-2,2-difluoro-3-hydroxy-4,4-dimethylpentanoate (13). Following the procedure outlined for the synthesis of the hydroxyester **12,** zinc powder (60 mg, 0.9 mmol), copper(I) chloride, ethyl bromodifluoroacetate **11** (0.11 mL, 0.59 mmol) and 3-benzyloxymethoxy-2,2-dimethylpropanal **9** (0.1 g, 0.45 mmol), after heating under reflux for 36 h and chromatography (85:15 light petroleum:EtOAc), gave the *title compound* **13** (0.12 g, 75%) as a colourless oil, R_f = 0.6 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 369.1483. $C_{17}H_{24}O_5F_2Na$ requires M, 369.1485); ν_{max}/cm^{-1} 3458, 2942, 2884, 1759, 1455, 1308, 1045, 910 and 740; δ_H (500 MHz, $CDCl_3$) 1.09 and 1.22 (each 3 H, s, 4-CH_3), 1.37 (3 H, t, *J* 7.5, OCH_2CH_3), 3.40 and 3.83 (each 1 H, d, *J* 7.5, 5-H), 3.93-4.02 (2 H, m, 3-H, OH), 4.36 (2 H, q, *J* 6.2, OCH_2), 4.61 and 4.62 (each 1 H, d, *J* 12.5, PhHC*H*), 4.76 and 4.77 (each 1 H, d, *J* 7.5, OHC*H*O) and 7.33-7.39 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 14.0, 18.2, 21.0, 24.2, 62.9, 69.9, 76.5, 76.8, 94.8, 117.0 (t, $^1J_{C\text{-}F}$ 261), 127.9, 128.5, 137.3 and 164.0 (t, $^2J_{C\text{-}F}$ 30); δ_F (376 MHz, $CDCl_3$) −124.57 and −105.93 (each d, $^2J_{F\text{-}F}$ 255.7*)*; *m/z* (ES^+) 369 (M^+ + 23, 100%).

Ethyl 5-*tert*-butyldiphenylsilyloxy-2,2-difluoro-3-hydroxy-4,4-dimethylpentanoate (14). The procedure outlined for the synthesis of the hydroxyester **12** using zinc powder (0.61 g, 9.4 mmol), copper(I) chloride, ethyl bromodifluoroacetate **11** (0.8 mL, 6.1 mmol) and 3-*tert*-butyldiphenylsilyloxy-2,2-dimethylpropanal **10** (1.6 g, 4.7 mmol), after heating under reflux for 36 h, an aqueous extraction using ether (15 mL), water (10 mL) and aqueous hydrogen chloride (1 M, 10 mL), and with extraction of the aqueous layer using ether (3 × 15 mL), gave, after chromatography (90:10 light petroleum:EtOAc), the *title compound* **14** (0.7 g, 78%) as a colourless oil, R_f = 0.7 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 487.2089. $C_{25}H_{34}O_4F_2SiNa$ requires M, 487.2087); ν_{max}/cm^{-1} 3445, 2931, 2858, 1761, 1724, 1428, 1305, 1110, 1071, 820 and 739; δ_H (400 MHz, $CDCl_3$) 1.10 [15 H, s, 2 × 4-CH_3, $SiC(CH_3)_3$], 1.39 (3 H, t, *J* 6.0, OCH_2CH_3), 3.40 and 3.89 (each 1 H, d, *J* 12.0, 5-H), 4.10 (1 H, d, *J* 24.0, 3-H), 4.39 (2 H, q, *J* 8.0, OCH_2), 7.38-7.44 (6 H, m, ArH) and 7.70-7.76 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.9, 19.1, 23.8, 26.5, 26.8, 29.7, 38.0, 62.8, 73.4, 117.0 (t, $^1J_{C\text{-}F}$ 258.0), 127.7, 127.8, 129.6, 130.0, 132.1, 134.8, 135.6, 135.7 and 164.1 (t, $^2J_{C\text{-}F}$ 31.5); *m/z* (ES^+) 487 (M^+ + 23, 100%).

Ethyl 5-(2-benzothiazolyl)sulfanyl-2,2-difluoro-4,4-dimethyl-3-triethylsilyloxypentanoate (15). 2,6-Lutidine (1.3 mL, 11 mmol) and triethylsilyl triflate (1.9 mL, 8.4 mmol) were added to the hydroxyester **12** (2.1 g, 5.6 mmol) in DCM (20 mL) at 0 °C and the mixture stirred at rt for 24 h. Water (20 mL) was added and the aqueous layer was extracted with DCM (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (80:20 light petroleum:EtOAc) gave the *title compound* **15** (2.05 g, 75%) as a yellow oil, R_f = 0.65 (70:30 light petroleum:EtOAc) (Found: M^+ + H, 490.1717. $C_{22}H_{34}NO_3F_2S_2Si$ requires M, 490.1712); ν_{max}/cm^{-1} 2955, 1758, 1459, 1427, 1307, 1082, 994, 830 and 726; δ_H (400 MHz, $CDCl_3$) 0.61-0.66 (6 H, m, 3 × $SiCH_2$), 0.93 (9 H, t, *J* 7.6, 3 × CH_2CH_3), 1.05 and 1.08 (each 3 H, s, 4-CH_3), 1.30 (3 H, t, *J* 6.8, OCH_2CH_3), 3.38 and 3.47 (each 1 H, d, *J* 10.0, 5-H), 4.13 (1 H, m, 3-H), 4.26 (2 H, q, *J* 6.8, OCH_2CH_3), 7.22 (1 H, t, *J* 8.4, ArH), 7.34 (1 H, t, *J* 7.6, ArH), 7.67 (1 H, d, *J* 8.0, ArH) and 7.77 (1 H, d, *J* 8.4, ArH); δ_C (125 MHz, $CDCl_3$) 5.4, 6.9, 13.9, 22.7, 23.3, 39.5, 42.8, 63.1, 76.8, 115.2 (t, $^1J_{C\text{-}F}$ 255.0), 121.0, 121.5, 124.2, 125.9, 135.2, 153.2, 164.2 (t, $^2J_{C\text{-}F}$ 33.2) and 167.3; δ_F (376 MHz, $CDCl_3$) −111.42 and −105.89 (each d, $^2J_{F\text{-}F}$ 263.2*)*; *m/z* (ES^+) 512 (M^+ + 23, 100%) and 490 (M^+ + 1, 61).

Ethyl 5-benzyloxymethoxy-2,2-difluoro-4,4-dimethyl-3-triethylsilyloxypentanoate (16). Following the procedure outlined for the preparation of the silyl ether **15**, the hydroxyester **13** (0.2 g, 0.58 mmol), 2,6-lutidine (0.2 mL, 1.7 mmol) and triethylsilyl triflate (0.2 mL, 0.87 mmol) with stirring for 10 d, after chromatography (85:15 light petroleum:EtOAc) gave the *title compound* **16** (0.24 g, 85%) as a colourless oil, R_f = 0.75 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 483.2337. $C_{23}H_{38}O_5F_2SiNa$ requires M, 483.2349); ν_{max}/cm^{-1} 2972, 2878, 1760, 1455, 1379, 1306, 1086, 1046, 879, 834 and 732; δ_H (500 MHz, $CDCl_3$) 0.65-0.69 (6 H, m, 3 × $SiCH_2$), 0.92-1.03 [15 H, m, 2 × 4-CH_3, 3 × $SiCH_2CH_3$), 1.37 (3 H, t, *J* 7.5, OCH_2CH_3), 3.31 and 3.44 (each 1 H, d, *J* 10.0, 5-H), 4.24-4.34 (3 H, m, 3-H, OCH_2), 4.58 and 4.62 (each 1 H, d, *J* 10.0,

PhHC*H*), 4.73 and 4.75 (each 1 H, d, *J* 5.0, OHC*H*O) and 7.32-7.37 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 5.1, 6.8, 13.8, 18.0, 20.5, 21.2, 38.9, 62.7, 69.3, 74.7, 75.1, 94.7, 115.7 (t, $^1J_{C\text{-}F}$ 261), 127.7, 127.8, 128.4, 137.8 and 164.4 (t, $^2J_{C\text{-}F}$ 30); δ_F (376 MHz) −111.35 and −106.22 (each d, $^1J_{F\text{-}F}$ 263.2*)*; *m/z* (ES^+) 483 (M^+ + 23, 75%) and 369 (100).

Ethyl 5-*tert*-butyldiphenylsilyloxy-2,2-difluoro-4,4-dimethyl-3-triethylsilyloxypentanoate (17). Following the procedure outlined for the preparation of the silyl ether **15**, the hydroxyester **14** (0.2 g, 0.43 mmol), 2,6-lutidine (0.12 mL, 1.0 mmol) and triethylsilyl triflate (0.2 mL, 0.86 mmol) with stirring for 10 days, after chromatography (85:15 light petroleum:EtOAc) gave the *title compound* **17** (0.23 g, 94%) as a colourless oil, R_f = 0.8 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 601.2957. $C_{31}H_{48}O_4F_2Si_2Na$ requires M, 601.2952); ν_{max}/cm^{-1} 2886, 1670, 1432, 1243 and 1032; δ_H (400 MHz, $CDCl_3$) 0.50-0.62 (6 H, m, 3 × $SiCH_2$), 0.88-0.97 (9 H, m, 3 × $SiCH_2CH_3$), 1.07-1.10 [15 H, s, 2 × 4-CH_3, $SiC(CH_3)_3$], 1.34 (3 H, t, *J* 7.0, OCH_2CH_3), 3.30 and 3.50 (each 1 H, d, *J* 12.0, 5-H), 4.27-4.39 (3 H, m, 3-H, OCH_2), 7.38-7.45 (6 H, m, ArH) and 7.64-7.67 (4 H, m, ArH); *m/z* (ES^+) 601 (M^+ + 23, 10%), 565 (50) and 487 (100).

6-(2-Benzothiazolyl)sulfanyl-3,3-difluoro-5,5-dimethyl-4-triethylsilyloxyhexan-2-one (18). Methyllithium (1.0 M, 4.0 mL, 4.0 mmol) was added to the ester **15** (1.3 g, 2.66 mmol) in THF (30 mL) at −78 °C and the solution was stirred at −78 °C for 5.5 h. Water (20 mL) was added followed by ether (20 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:EtOAc) gave the *title compound* **18** (0.93 g, 77%) as a yellow oil, R_f = 0.7 (70:30 light petroleum:EtOAc) (Found: M^+ + H, 460.1617. $C_{21}H_{32}NO_2F_2S_2Si$ requires M, 460.1607); δ_H (400 MHz, $CDCl_3$) 0.61-0.67 (6 H, m, 3 × $SiCH_2$), 0.93 (9 H, t, *J* 8.4, 3 × $SiCH_2CH_3$), 1.03 and 1.05 (each 3 H, s, 5-CH_3), 2.32 (3 H, t, *J* 1.8, 1-H_3), 3.49 and 3.53 (each 1 H, d, *J* 12.0, 6-H), 4.14 (1 H, t, *J* 12.8, 4-H), 7.21 (1 H, td, *J* 8.4, 1.2, ArH), 7.33 (1 H, td, *J* 7.8, 1.2, ArH), 7.67 (1 H, d, *J* 7.8, ArH) and 7.77 (1 H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 5.1, 6.9, 23.1, 23.5, 26.2, 31.0, 39.4, 42.7, 76.6, 116.9, 121.0, 121.4, 124.2 126.0, 135.3, 153.1, 167.3 and 199.6 (d, $^2J_{C\text{-}F}$ 30); δ_F (376 MHz, $CDCl_3$) −110.73 and −107.56 (each d, $^2J_{F\text{-}F}$ 270.7); *m/z* (ES^+) 482 (M^+ + 23, 100%) and 460 (M^+ + 1, 55).

Methyllithium (1.0 M, 0.07 mL, 0.7 mmol) was added to the ester **15** (0.13 g, 0.27 mmol) in THF (2 mL) at 0 °C and the solution was stirred at rt for 1.5 h. Water (10 mL) was added followed by ether (10 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (80:20 light petroleum:ether) gave 6-(2-benzothiazolyl)sulfanyl-3,3-difluoro-4-triethylsilyloxy-2,5,5-trimethylhexan-2-ol (86 mg, 72%) as a colourless oil, R_f = 0.5 (70:30 light petroleum:EtOAc) (Found: M^+ + H, 476.1922. $C_{22}H_{36}NO_2F_2S_2Si$ requires M, 476.1920); ν_{max}/cm^{-1} 3452, 2954, 1536, 1458, 1428, 1238, 1159, 1070, 1003 and 740; δ_H (500 MHz, $CDCl_3$) 0.44-0.46 (6 H, m, 3 × $SiCH_2$), 0.74 (9 H, t, *J* 10.0, 3 × CH_2CH_3), 1.14 and 1.19 (each 3 H, s, 5-CH_3), 1.28 and 1.31 (each 3 H, s, 1-H_3 or 2-CH_3), 3.01 and 3.86 (each 1 H, d, *J* 15.0, 6-H), 4.15 (1 H, dd, *J* 20.0, 5.0, 4-H), 5.56 (1 H, d, *J* 5.0, OH), 7.22 and 7.34 (each 1 H, t, *J* 10.0, ArH) and 7.66 and 7.73 (each 1 H, d, *J* 10.0, ArH); δ_F (376 MHz, $CDCl_3$) −124.40 and −113.61 (each d, $^2J_{F\text{-}F}$ 225.6); *m/z* (ES^+) 476 (M^+ + 1, 100%).

6-Benzyloxymethyloxy-3,3-difluoro-5,5-dimethyl-4-triethylsilyloxyhexan-2-one (19). Following the procedure outlined for the synthesis of the ketone **18**, the ester **16** (50 mg, 0.11 mmol) in THF (2 mL) and methyllithium (1.0 M, 0.16 mL, 0.16 mmol), after chromatography (90:10 light petroleum: EtOAc) gave the *title compound* **19** (44 mg, 86%) as a yellow oil, R_f = 0.7 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 453.2245. $C_{22}H_{36}O_4F_2SiNa$ requires M, 453.2244); ν_{max}/cm^{-1} 2993, 2864, 1783, 1432, 1304, 1048, 1032 and 728; δ_H (400 MHz, $CDCl_3$) 0.53-0.82 (6 H, m, 3 × $SiCH_2$), 0.93-1.03 (15 H, m, 2 × 5-CH_3, 3 × CH_2CH_3), 2.36 (3 H, s, 1-H_3), 3.34 and 3.37 (each 1 H, d, *J* 8.0, 6-H), 4.26 (1 H, m, 4-H), 4.56 and 4.62 (each 1 H, d *J* 12.0, PhHC*H*), 4.70 and 4.72 (each 1 H, d *J* 8.0, OHC*H*O) and 7.27-7.38 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 5.0, 6.8, 17.9, 20.9, 21.6, 26.0, 38.8, 69.4, 74.2, 74.8 (t, $^2J_{C\text{-}F}$ 24), 94.5, 117.1 (t, $^1J_{C\text{-}F}$ 257.0), 127.7, 127.8, 128.4, 137.7 and 199.4 (t, $^2J_{C\text{-}F}$ 30.5); δ_F (376 MHz, $CDCl_3$) −109.85 and −108.48 (each d, $^2J_{F\text{-}F}$, 270.7); *m/z* (ES^+) 453 (M^+ + 23, 100%).

6-*tert*-Butyldiphenylsilyloxy-3,3-difluoro-5,5-dimethyl-4-triethylsilyloxyhexan-2-one (20). Following the procedure outlined for the synthesis of the ketone **18,** the ester **17** (0.5 g, 0.8 mmol) in THF (20 mL) and methyllithium (1.0 M, 1.3 mL, 1.3 mmol), after chromatography (90:10 light petroleum: EtOAc) gave the *title compound* **20** (0.22 g, 55%) as a colourless oil, R_f = 0.8 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 571.2854. $C_{30}H_{46}O_3F_2Si_2Na$ requires M, 571.2846); ν_{max}/cm^{-1} 2980, 1724, 1423, 1201 and 1109; δ_H (500 MHz, $CDCl_3$) 0.55-0.65 (6 H, m, 3 × $SiCH_2$), 0.92 (9 H, t, *J* 6.0, 3 × $SiCH_2CH_3$), 1.09 (3 H, s, 5-CH_3), 1.12 [9 H, s, $SiC(CH_3)_3$], 1.28 (3 H, s, 5-CH_3), 2.34 (3 H, s, 1-H_3), 3.35 and 3.48 (each 1 H, d, *J* 10.0, 6-H), 4.35 (1 H, t, *J* 10.0, 4-H), 7.37-7.44 (6 H, m, ArH) and 7.66-7.68 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 6.5, 6.9, 19.2, 19.4, 20.9, 26.2, 26.9, 40.1, 70.0, 74.3 (t, $^2J_{C\text{-}F}$ 32), 127.4, 127.6, 134.3, 134.4, 135.1, 135.5, 135.8, 135.9 and 199.8 (t, $^2J_{C\text{-}F}$ 30); *m/z* (ES^+) 571 (M^+ + 23, 100%).

6-Benzyloxymethoxy-3,3-difluoro-4-triethylsilyloxy-2,5,5-trimethylhex-1-ene (21). Potassium hexamethyldisilazide (1.0 M in THF, 0.5 mL, 0.5 mmol) was added to methyl(triphenyl)phosphonium bromide (0.2 g, 0.56 mmol) in toluene (2 mL) at 0 °C and the solution was stirred for 30 min. The ketone **19** (80 mg, 0.19 mmol) in toluene (1 mL) was added and the mixture was stirred at rt for 48 h. Water (2 mL) was added followed by EtOAc (5 mL) and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:ether) gave the *title compound* **21** (60 mg, 75%) as a colourless oil, R_f = 0.9 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 451.2458. $C_{23}H_{38}O_3F_2SiNa$ requires M, 451.2451);

ν_{max}/cm^{-1} 2954, 2877, 1455, 1379, 1239, 1159, 1105, 1047, 1025, 1002, 921, 833 and 729; δ_H (500 MHz, $CDCl_3$) 0.65-0.71 (6 H, m, 3 × $SiCH_2$), 0.96-1.03 (15 H, m, 2 × 5-CH_3, 3 × CH_2CH_3), 1.91 (3 H, s, 2-CH_3), 3.31 and 3.41 (each 1 H, d, *J* 10.0, 6-H), 4.05 (1 H, t, *J* 12.0, 4-H), 4.57 and 4.64 (each 1 H, d, *J* 10.0, PhHC*H*), 4.74 and 4.75 (each H, d, *J* 7.0, OHC*H*O), 5.15 and 5.40 (each 1 H, s, 1-H) and 7.28-7.37 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 5.0, 7.0, 19.1, 20.6, 21.1, 30.3, 38.8, 69.3, 75.0, 76.6 (t, $^2J_{C\text{-}F}$ 24.0), 94.7, 116.2 (t, $^3J_{C\text{-}F}$ 9.0), 121.3 (t, $^1J_{C\text{-}F}$ 245.6), 127.7, 127.8, 128.4, 137.9 and 140.6 (t, $^2J_{C\text{-}F}$ 24.0); δ_F (376 MHz, $CDCl_3$) −98.90 and −98.69 (each d, $^2J_{F\text{-}F}$ 244); *m/z* (ES^+) 451 (M^+ + 23, 100%).

6-*tert*-Butyldiphenylsilyloxy-3,3-difluoro-4-triethylsilyloxy-2,5,5-trimethylhex-1-ene (22). Following the procedure outlined for the synthesis of the alkene **21,** methyl(triphenyl)phosphonium bromide (0.16 g, 0.45 mmol) in toluene (2 mL), potassium hexamethyldisilazide (1.0 M in THF, 0.41 mL, 0.41 mmol) and the ketone **20** (84 mg, 0.15 mmol) in toluene (1 mL), after chromatography (90:10 light petroleum:EtOAc) gave the *title compound* **22** (61 mg, 73%) as a colourless oil, R_f = 0.9 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 569.3050. $C_{31}H_{48}O_2F_2Si_2Na$ requires M, 569.3054); ν_{max}/cm^{-1} 2955, 1466, 1107 and 826; δ_H (400 MHz, $CDCl_3$) 0.55-0.67 (6 H, m, 3 × $SiCH_2$), 0.92-0.98 (9 H, m, 3 × $SiCH_2CH_3$), 1.11 (3 H, s, 5-CH_3), 1.13 [9 H, s, $SiC(CH_3)_3$], 1.30 (3 H, s, 5-CH_3), 1.89 (3 H, s, 2-CH_3), 3.40 and 3.51 (each 1 H, d, *J* 8.0, 6-H), 4.09 (1 H, t, *J* 8.0, 4-H), 5.08 and 5.33 (each 1 H, s, 1-H), 7.35-7.48 (6 H, m, ArH) and 7.68-7.73 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 6.9, 7.0, 19.1, 19.3, 20.5, 26.9, 40.3, 70.2, 72.9, 74.1, 116.1, 121.2 (t, $^2J_{C\text{-}F}$ 23), 127.4, 128.6, 129.6, 132.0, 135.7, 137.3 and 140.6; δ_F (376 MHz, $CDCl_3$) −98.9 and −98.2 (t, $^2J_{F\text{-}F}$ 248*)*; *m/z* (ES^+) 569 (M^+ + 23, 20%) and 293 (100).

2-Bromomethyl-6-*tert*-butyldiphenylsilyloxy-3,3-difluoro-4-triethylsilyloxy-5,5-dimethylhex-1-ene (23). *N*-Bromosuccinimide (12 mg, 0.065 mmol) was added to the alkene **22** (30 mg, 0.055 mmol) in chloroform (1 mL). The suspension was exposed to UV light for 10 min and then heated under reflux for 24 h. After cooling to rt, the mixture was concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:EtOAc) gave the *title compound* **23** (25 mg, 72%) as a colourless oil, R_f = 0.9 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 647.2169. $C_{31}H_{47}O_2{}^{79}BrF_2Si_2Na$ requires M, 647.2159; Found: M^+ + Na, 649.1790. $C_{31}H_{47}O_2{}^{81}BrF_2Si_2Na$ requires M, 649.2159); ν_{max}/cm^{-1} 2956, 2876, 1471, 1428, 1107, 1078, 1006, 822, 739 and 700; δ_H (400 MHz, $CDCl_3$) 0.57-0.64 (6 H, m, 3 × $SiCH_2$), 0.88-0.96 (9 H, m, 3 × $SiCH_2CH_3$], 1.08 [9 H, s, $SiC(CH_3)_3$], 1.11 and 1.27 (each 3 H, s, 5-CH_3), 3.32-3.49 (2 H, m, 6-H_2), 4.06-4.11 (3 H, m, 4-H, 2-CH_2), 5.67-5.70 (2 H, m, 1-H_2), 7.38-7.45 (6 H, m, ArH) and 7.64-7.72 (4 H, m, ArH); δ_F (376 MHz, $CDCl_3$) −98.96 and −91.89 (each d, $^2J_{F\text{-}F}$ 256); *m/z* (ES^+) 649 (M^+ + 23, 20%), 647 (M^+ + 23, 5) and 258 (100).

2-Iodo-4-*tert*-butyldimethylsilyloxyhex-1-ene (29). Trimethylsilyl chloride (0.52 mL, 4.0 mmol) and water (0.037 mL, 2.0 mmol) were added to sodium iodide (0.62 g, 4.0 mmol) in acetonitrile (4 mL) and the yellow suspension was stirred at rt for 20 min. Hex-5-yn-3-ol **27** (0.2 mL, 1.8 mmol) in acetonitrile (1 mL) was added dropwise and the mixture stirred for 4 h. Water (5 mL) was added and the mixture was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum to 90:10 light petroleum:EtOAc) gave 5-iodohex-5-en-3-ol **28** (0.33 g, 80%) as a colourless oil, R_f = 0.55 (70:30 light petroleum:EtOAc); ν_{max}/cm^{-1} 3402, 2964, 2933, 1710, 1617, 1461, 1205, 1113, 1021, 979 and 899; δ_H (400 MHz, $CDCl_3$) 1.00 (3 H, t, *J* 8.0, 1-H_3), 1.56 (2 H, m, 2-H_2), 1.63 (1 H, br. s, OH), 2.46 (1 H, dd, *J* 12.0, 8.0, 4-H), 2.56 (1 H, dd, *J* 12.0, 3.0, 4-H'), 3.82 (1 H, m, 3-H) and 5.86 and 6.18 (each 1 H, s, 6-H); δ_C (100 MHz, $CDCl_3$) 9.9, 28.9, 52.4, 71.3, 107.7 and 128.7.

Imidazole (0.21 g, 3.1 mmol) and *tert*-butyldimethylsilyl chloride (0.26 g, 1.7 mmol) were added to 5-iodohex-5-en-3-ol **28** (0.32 g, 1.4 mmol) in DCM (10 mL) and the solution stirred at rt for 24 h. Water (10 mL) was added, the aqueous layer was extracted with DCM (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:EtOAc) gave the *title compound* **29** (0.36 g, 75%) as a pale yellow oil, R_f = 0.6 (70:30 light petroleum:EtOAc); ν_{max}/cm^{-1} 2956, 2928, 2856, 1618, 1462, 1361, 1252, 1101, 1033, 894, 835 and 774; δ_H (300 MHz, $CDCl_3$) 0.09 and 0.10 (each 3 H, s, $SiCH_3$), 0.87-0.90 [12 H, m, 6-H_3, $SiC(CH_3)_3$], 1.44-1.56 (2 H, m, 5-H_2), 2.47-2.51 (2 H, m, 3-H_2), 3.86 (1 H, m, 4-H) and 5.74 and 6.07 (each 1 H, s, 1-H); δ_C (100 MHz, $CDCl_3$) −4.6, −4.4, 9.2, 18.1, 25.8, 29.1, 52.4, 71.8, 108.7 and 127.8.

Ethyl 5-*tert*-butyldimethylsilyloxy-2,2-difluoro-3-methyleneheptanoate (30). Copper powder (65 mg, 1.02 mmol) was added to a vigorously stirred solution of ethyl 2-iodo-2,2-difluoroacetate **25** (0.025 mL, 0.170 mmol) in anhydrous DMSO (0.20 mL). After 3 h, the alkenyl iodide **29** (19 mg, 0.057 mmol) in anhydrous DMSO (0.20 mL) was added and the mixture stirred 1.25 h. A mixture of ice and saturated aqueous ammonium chloride (1:1, 10 mL) was added followed by ether (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the organic extracts were filtered through Celite® using ether (20 mL). The filtrate was washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using base-washed silica (0.5:99.5 to 1:99 ether:light petroleum) gave the *title compound* **30** (8 mg, 0.024 mmol, 8%) as a colourless oil, R_f = 0.27 (1:99 ether:light petroleum) (Found: M^+ + H, 337.2005. $C_{16}H_{31}O_3F_2Si$ requires M, 337.2005); ν_{max}/cm^{-1} 2958, 2929, 2857, 1768, 1464, 1372, 1292, 1255, 1077, 1006, 837 and 775; δ_H (500 MHz, $CDCl_3$) 0.05 (6 H, s, 2 × $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.90 (3 H, t, *J* 7.0, 7-H_3), 1.35 (3 H, t, *J* 7.0, OCH_2CH_3), 1.40-1.56 (2 H, m, 6-H_2), 2.31 (2 H, d, *J* 6.2, 4-H_2), 3.80 (1 H, pent, *J* 6.2, 5-H), 4.33 (2 H, q, *J* 7.0, OCH_2) and 5.40 and 5.60 (each 1 H, t, *J* 1.9, 3-CH); δ_C (125 MHz, $CDCl_3$) −4.6, −4.5, 9.2, 13.9, 18.0, 25.9, 29.4, 37.7, 63.0, 71.5, 114.0 (t, $^1J_{C\text{-}F}$ 252.1), 120.5 (t, $^3J_{C\text{-}F}$ 8.2), 137.7 (t, $^2J_{C\text{-}F}$ 22.8) and 163.9 (t, $^2J_{C\text{-}F}$ 34.6); δ_F (471 MHz, $CDCl_3$) −106.99 and −105.25 (both d, $J_{F\text{-}F}$ 253.4); *m/e* (ES^+) 359.2 (M^+ + 23, 50%) and 210.2 (100). This capricious reaction required copper powder that was very fine, bronze-pink in colour and extremely lustrous, anhydrous solvent and vigorous stirring, to generate the active copper-reagent species.

This procedure gave ethyl (*E*)-2,2-difluoro-5-*tert*-butyldimethylsilyloxy-3-(*tert*-butyldimethylsilyloxymethyl)pent-3-enoate **33** (3 mg, 0.007 mmol, 12%) as a colourless oil (Found: M^+ + H, 439.2510. $C_{20}H_{41}O_4F_2Si_2$ requires M, 439.2511); ν_{max}/cm^{-1} 2954, 2931, 2886, 2858, 1769, 1472, 1255, 1095, 836 and 778; δ_H (400 MHz, $CDCl_3$) 0.07 and 0.09 (each 6 H, s, 2 × $SiCH_3$), 0.89 and 0.91 [each 9 H, s, $SiC(CH_3)_3$], 1.34 (3 H, t, *J* 7.3, OCH_2CH_3), 4.29 (2 H, s, 3-CH_2), 4.29 (2 H, q, *J* 7.3, OCH_2CH_3), 4.39-4.42 (2 H, m, 5-H_2) and 6.39 (1 H, t, *J* 6.3, 4-H); δ_C (100 MHz, $CDCl_3$) −5.7, −5.3, 13.9, 18.3(2), 25.8, 25.9, 57.4, 59.7, 62.7, 113.0 (t, $^1J_{C\text{-}F}$ 251.1), 130.6 (t, $^2J_{C\text{-}F}$ 21.4), 135.6 (t, $^3J_{C\text{-}F}$ 8.8) and 163.6 (t, $^2J_{C\text{-}F}$ 34.6); δ_F (377 MHz, $CDCl_3$) −106.47; *m/z* (ES^+) 461.3 (M^+ + 23, 100%).

This procedure gave ethyl (*E*)-2,2-difluoro-5-*tert*-butyldiphenylsilyloxy-3-(*tert*-butyldiphenylsilyloxymethyl)pent-3-enoate **34** (4 mg, 0.006 mmol, 14%) as a colourless oil, R_f = 0.39 (5:95 ether:light petroleum); ν_{max}/cm^{-1} 3072, 2957, 2930, 2857, 1769, 1472, 1428, 1290, 1112, 1022, 844, 740 and 702; δ_H (400 MHz, $CDCl_3$) 0.92 and 1.01 [each 9 H, s, $SiC(CH_3)_3$], 1.29 (3 H, t, *J* 7.0, OCH_2CH_3), 4.02 (2 H, s, 3-CH_2), 4.21-4.28 (4 H, m, 5-H_2, OCH_2CH_3), 6.32 (1 H, t, *J* 5.6, 4-H), 7.26-7.44 (12 H, m, ArH) and 7.53 and 7.59 (each 4 H, dd, *J* 8.0, 1.5, ArH); δ_F (377 MHz, $CDCl_3$) −105.74; *m/z* (ES^+) 704.5 (M^+ + 18, 100%).

2-Difluoromethylenedecan-1-ol (54). Methyllithium (1.6 M in ether, 0.37 mL, 0.60 mmol) was added dropwise to the ketone **52**[28] (68 mg, 0.30 mmol) and di-iodomethane (0.048 mL, 0.60 mmol) in dry THF (1.8 mL) at −78 °C and the mixture allowed to warm to rt over 30 min then cooled to −78 °C. *tert*-Butyllithium (1.7 M in pentane, 5.15 mmol, 3.03 mL) was added and the mixture was stirred at rt for 16 h. Aqueous hydrogen chloride (1 M, 20 mL) and ether (20 mL) were added and the aqueous phase was extracted with ether (3 × 20 mL). The organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:99 to 5:95 ether:light petroleum) gave the *title compound* **54** (94 mg, 0.46 mmol, 44%) as a colourless oil, R_f = 0.18 (10:90 ether:light petroleum) (Found: M^+, 206.1477. $C_{11}H_{20}OF_2$ requires M, 206.1477); ν_{max}/cm^{-1} 3333, 2955, 2925, 2856, 1746, 1466, 1264, 1001 and 730; δ_H (500 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7.0, 10-H_3), 1.20-1.35 (10 H, m, 5 × CH_2), 1.40-1.48 (2 H, m, 4-H_2), 1.96 (1 H, br. s, OH), 2.09 (2 H, m, 3-H_2) and 4.14 (2 H, s, 1-H_2); δ_C (125 MHz, $CDCl_3$) 14.0, 22.6, 24.4, 27.5, 29.2(2), 29.3, 31.8, 57.7, 90.0 (dd, $^2J_{C\text{-}F}$ 16.4, 13.7) and 154.2 (t, $^1J_{C\text{-}F}$ 288.5); δ_F (377 MHz, $CDCl_3$) −93.14 and −92.87 (both d, $^2J_{F\text{-}F}$ 48.1).

1-Bromo-2-(difluoromethylene)decane (55). Dimethyl sulfide (0.094 mL, 1.280 mmol) was added to *N*-bromosuccinimide (0.185 g, 1.04 mmol) in dry DCM (4.0 mL) at 0 °C and the mixture stirred for 10 min then cooled to −20 °C. The alcohol **54** (0.143 g, 0.693 mmol) in DCM (3 mL) was added and the mixture stirred at rt for 16 h. Saturated aqueous sodium hydrogen carbonate (10 mL) and DCM (10 mL) were added and the aqueous phase was extracted with DCM (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum) gave the *title compound* **55** (0.12 g, 0.435 mmol, 63%) as a colourless oil, R_f = 0.41 (light petroleum); ν_{max}/cm^{-1} 2956, 2925, 2856, 1735, 1465, 1290, 1223, 1188 and 1058; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.0, 10-H_3), 1.25-1.35 (10 H, m, 5 × CH_2), 1.46 (2 H, m, 4-H_2), 2.14 (2 H, m, 3-H_2) and 4.02 (2 H, t, $^4J_{H\text{-}F}$ 1.9, 1-H_2); δ_C (125 MHz, $CDCl_3$) 14.0, 22.6, 25.2, 27.1(m), 27.8 (dd, $^3J_{C\text{-}F}$ 7.4, 1.8), 29.1, 29.2, 29.3, 31.8, 89.0 (dd, $^2J_{C\text{-}F}$ 22.0, 12.9) and 153.9 (t, $^1J_{C\text{-}F}$ 291.2); δ_F (377 MHz, $CDCl_3$) −89.64 and −88.32 (both d, $^2J_{F\text{-}F}$ 35.5).

Following this procedure, *N*-bromosuccinimide (63 mg, 0.36 mmol) in DCM (1.38 mL), dimethyl sulfide (0.032 mL, 0.44 mmol) and the alcohol **54** (49 mg, 0.237 mmol) in DCM (1 mL) with heating the crude product in toluene-d_8 (0.5 mL) under reflux for 16 h gave, after chromatography (light petroleum) a mixture (57 mg, 0.212 mmol, 89%) of the title compound **55** and 2-(bromodifluoromethyl)dec-1-ene **56** as a colourless oil, **55**:**56** = 20:80; ν_{max}/cm^{-1} 2956, 2926, 2856, 1738, 1465, 1131, 1114, 1101, 926 and 895; δ_H (500 MHz, $CDCl_3$) isomer **56** 0.90 (3 H, t, *J* 6.9, 10-H_3), 1.25-1.41 (10 H, m, 5 × CH_2), 1.56 (2 H, m, 4-H_2), 2.28 (2 H, t, *J* 7.9, 3-H_2), 5.17 (1 H, t, $^4J_{H\text{-}F}$ 1.6, 1-H) and 5.60 (1 H, t, $^4J_{H\text{-}F}$ 1.0, 1-H'); δ_C (125 MHz, $CDCl_3$) 14.1, 22.7, 27.4, 29.2(2), 29.2, 29.4, 29.7, 31.8, 114.3 (t, $^3J_{C\text{-}F}$ 7.4), 119.7 (t, $^1J_{C\text{-}F}$ 306.7) and 145.4 (t, $^2J_{C\text{-}F}$ 19.3); δ_F (377 MHz, $CDCl_3$) −48.43.

Difluorinated alcohols 57: general procedure. Indium powder (43 mg, 0.37 mmol) was added to a vigorously stirred solution of 1-bromo-2-(difluoromethylene)decane **55** (50 mg, 0.19 mmol) in DMF (1.0 mL) in a 10 mL Schlenk tube. After 10 min, the aldehyde (0.41 mmol) was added and the mixture stirred for 14 h. Aqueous hydrogen chloride (10%, 10 mL) and ether (10 mL) were added and the aqueous phase was extracted with ether (3 × 30 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum to 5:95 ether:light petroleum) gave the alcohols **57** as colourless oils.

2,2-Difluoro-3-methylene-1-phenylundecan-1-ol **57a**. (46 mg, 0.155 mmol, 84%), R_f = 0.14 (10:90 ether:light petroleum) (Found: M^+ + NH_4, 314.2285. $C_{18}H_{30}NOF_2$ requires M, 314.2290; ν_{max}/cm^{-1} 3380, 2954, 2925, 2855, 1455, 1164, 1086, 1060, 1026, 920 and 743; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.0, 11-H_3), 1.23-1.33 (10 H, m, 5 × CH_2), 1.43 (2 H, m, 5-H_2), 1.89-2.00 (2 H, m, 4-H_2), 2.43 (1 H, br. s, OH), 4.93 (1 H, t, $^3J_{H\text{-}F}$ 11.0, 1-H), 5.18 and 5.31 (each 1 H, s, 3-CH), 7.33-7.38 (3 H, m, ArH) and 7.40-7.44 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 27.6, 29.2(2), 29.3, 30.5 (t, $^3J_{C\text{-}F}$ 2.9), 31.8, 75.4 (t, $^2J_{C\text{-}F}$ 30.0), 116.3 (t, $^3J_{C\text{-}F}$ 8.0), 121.2 (t, $^1J_{C\text{-}F}$ 247.2), 127.8, 128.1, 128.6, 136.1 (t, $^3J_{C\text{-}F}$ 2.2) and 142.8 (t, $^2J_{C\text{-}F}$ 22.6); δ_F (471 MHz, $CDCl_3$) −109.53; *m/z* (APCI) 314.2 (M^+ + 18, 100%).

2,2-Difluoro-3-methylene-1-(4-methoxyphenyl)undecan-1-ol **57b**. (40 mg, 0.12 mmol, 65%), R_f = 0.65 (50:50 ether:light petroleum) (Found: M^+ + NH_4, 344.2390. $C_{19}H_{32}NO_2F_2$ requires M, 344.2396); ν_{max}/cm^{-1} 3457, 2925, 2855, 1613, 1514, 1464, 1249, 1174, 1062, 1032, 921, 855 and 794; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.0, 11-H_3), 1.23-1.35 (10 H, m, 5 × CH_2), 1.43 (2 H, m, 5-H_2), 1.89-2.01 (2 H, m, 4-H_2), 2.48 (1 H, br. s, OH), 3.82 (3 H, s, OCH_3), 4.87 (1 H, t, $^3J_{H\text{-}F}$ 11.4, 1-H), 5.18 and 5.31 (each 1 H, s, 3-CH), 6.89 (2 H, d, *J* 8.9, ArH) and 7.34 (2 H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 27.6, 29.2(2),

29.4, 30.5 (t, $^3J_{C\text{-}F}$ 2.9), 31.8, 55.2, 75.1 (t, $^2J_{C\text{-}F}$ 29.9), 113.5, 116.2 (t, $^3J_{C\text{-}F}$ 8.8), 121.2 (t, $^1J_{C\text{-}F}$ 247.2), 128.2 (t, $^3J_{C\text{-}F}$ 2.2), 129.0, 142.9 (t, $^2J_{C\text{-}F}$ 22.6) and 159.8; δ_F (471 MHz, $CDCl_3$) −109.52 and −110.20 (both d, $^2J_{F\text{-}F}$ 244.7); *m/z* (GC/MS-CI) 327 ($M^+ + 1$).

2,2-Difluoro-3-methylene-1-(3-chlorophenyl)undecan-1-ol **57c**. (60 mg, 0.17 mmol, 93%), R_f = 0.2 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 348.1897. $C_{18}H_{29}NO^{35}ClF_2$ requires M, 348.1900); ν_{max}/cm^{-1} 3428, 2954, 2926, 2855, 1599, 1576, 1467, 1433, 1199, 1163, 1079, 925 and 776; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 6.8, 11-H_3), 1.22-1.36 (10 H, m, 5 × CH_2), 1.44 (2 H, m, 5-H_2), 1.96 (2 H, t, *J* 8.0, 4-H_2), 2.56 (1 H, br. s, OH), 4.90 (1 H, t, $^3J_{H\text{-}F}$ 10.8, 1-H), 5.22 and 5.32 (each 1 H, s, 3-CH), 7.26-7.35 (3 H, m, ArH) and 7.42-7.44 (1 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 27.6, 29.2, 29.4, 30.5 (t, $^3J_{C\text{-}F}$ 2.9), 31.8, 74.8 (t, $^2J_{C\text{-}F}$ 30.0), 116.7 (t, $^3J_{C\text{-}F}$ 8.1), 120.9 (t, $^1J_{C\text{-}F}$ 250.4), 126.0, 128.0, 128.8, 129.3, 134.1, 138.0 (t, $^3J_{C\text{-}F}$ 1.5) and 142.4 (t, $^2J_{C\text{-}F}$ 22.8); δ_F (471 MHz, $CDCl_3$) −109.99 and −108.92 (both d, $^2J_{F\text{-}F}$ 244.7); *m/z* (APCI) 348.2 ($M^+ + 18$, 100%).

5,5-Difluoro-6-methylenetetradecan-4-ol **57d**. (50 mg, 0.18 mmol, 98%), R_f = 0.23 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 280.2442. $C_{15}H_{32}NOF_2$ requires M, 280.2446); ν_{max}/cm^{-1} 3387, 2959, 2926, 2856, 1466, 1185, 1075, 1029, 964 and 922; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.6, 14-H_3), 0.96 (3 H, t, *J* 7.0, 1-H_3), 1.21-1.38 (10 H, m, 5 × CH_2), 1.38-1.70 (6 H, m, 3 × CH_2), 1.85 (1 H, br. s, OH), 2.04-2.19 (2 H, m, 7-H_2), 3.83 (1 H, q, *J* 9.6, 4-H) and 5.23 and 5.44 (each 1 H, s, 6-CH); δ_C (100 MHz, $CDCl_3$) 13.8, 14.1, 18.8, 22.6, 27.8, 29.2, 29.3, 29.4, 30.5 (t, $^4J_{C\text{-}F}$ 2.9), 31.8, 31.9 (t, $^3J_{C\text{-}F}$ 2.2), 72.3 (t, $^2J_{C\text{-}F}$ 28.7), 115.5 (t, $^3J_{C\text{-}F}$ 8.8), 121.8 (t, $^1J_{C\text{-}F}$ 247.5) and 142.9 (t, $^2J_{C\text{-}F}$ 22.8); δ_F (470 MHz, $CDCl_3$) −112.29 and −111.60 (both d, $^2J_{F\text{-}F}$ 246.3); *m/z* (APCI) 280.2 ($M^+ + 18$, 100%).

4,4-Difluoro-2-methyl-5-methylenetridecan-3-ol **57e**. (33 mg, 0.126 mmol, 68%), R_f = 0.39 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 280.2443. $C_{15}H_{32}NOF_2$ requires M, 280.2446); ν_{max}/cm^{-1} 3458, 2958, 2926, 2856, 1467, 1264, 1186, 1077, 1021, 907 and 725; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.8, 13-H_3), 0.99 and 1.05 (each 3 H, d, *J* 6.9, 1-H_3 or 2-CH_3), 1.23-1.38 (10 H, m, 5 × CH_2), 1.51 (2 H, m, 7-H_2), 1.82 (1 H, br. s, OH), 1.98 (1 H, m, 2-H), 2.05-2.19 (2 H, m, 6-H_2), 3.66 (1 H, m, 3-H) and 5.22 and 5.47 (each 1 H, s, 5-H); δ_C (100 MHz, $CDCl_3$) 14.1, 16.2 (t, $^4J_{C\text{-}F}$ 2.2), 20.8 (t, $^4J_{C\text{-}F}$ 1.5), 22.6, 27.8, 28.3, 29.2, 29.3, 29.4, 30.4 (t, $^3J_{C\text{-}F}$ 3.0), 31.8, 76.2 (t, $^2J_{C\text{-}F}$ 27.3), 115.1 (t, $^3J_{C\text{-}F}$ 9.6), 122.3 (t, $^1J_{C\text{-}F}$ 248.2) and 143.4 (t, $^2J_{C\text{-}F}$ 22.8); δ_F (471 MHz, $CDCl_3$) −109.36 and −108.49 (both d, $^2J_{F\text{-}F}$ 248.2); *m/z* (APCI) 280.2 ($M^+ + 18$, 100%).

4,4-Difluoro-2,2-dimethyl-5-methylenetridecan-3-ol **57f**. (24 mg, 0.087 mmol, 47%), R_f = 0.29 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 294.2602. $C_{16}H_{34}NOF_2$ requires M, 294.2603); ν_{max}/cm^{-1} 3491, 2957, 2925, 2856, 1741, 1714, 1466, 1368, 1166, 1057, 1016 and 922; δ_H (500 MHz, $CDCl_3$) 0.84-0.92 (3 H, m, 13-H_3), 1.07 [9 H, s, $C(CH_3)_3$], 1.23-1.38 (10 H, m, 5 × CH_2), 1.52 (2 H, m, 7-H_2), 1.83 (1 H, br. s, OH), 2.15 (2 H, t, *J* 7.9, 6-H_2), 3.52 (1 H, dd, $^3J_{H\text{-}F}$ 19.9, 6.3, 3-H), 5.21 (1 H, d, $^4J_{H\text{-}F}$ 1.6, 5-CH) and 5.47 (1 H, d, $^4J_{H\text{-}F}$ 2.5, 5-H'); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 26.9 (t, $^4J_{C\text{-}F}$ 2.2), 27.8, 29.2, 29.4(2), 30.5 (dd, $^3J_{C\text{-}F}$ 3.7, 2.2), 31.9, 34.8, 78.1 (dd, $^2J_{C\text{-}F}$ 29.5, 26.5), 114.8 (dd, $^3J_{C\text{-}F}$ 10.3, 8.1), 123.0 (dd, $^1J_{C\text{-}F}$ 253.4, 249.0) and 144.7 (t, $^2J_{C\text{-}F}$ 22.8); δ_F (471 MHz, $CDCl_3$) −111.59 and −100.68 (both d, $^2J_{F\text{-}F}$ 249.9); *m/z* (ES^+) 277.3 ($M^+ + 1$, 20%).

1-tert-Butyldiphenylsilyloxy-4,4-difluoro-5-methylenetridecan-3-ol **57g**. (85 mg, 0.169 mmol, 91%), R_f = 0.27 (10:90 ether:light petroleum) (Found: $M^+ + H$, 503.3138. $C_{30}H_{45}O_2F_2Si$ requires M, 503.3151); ν_{max}/cm^{-1} 3471, 2956, 2928, 2856, 1427, 1106, 1084, 936, 822 and 737; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 8.6, 13-H_3), 1.06 [9 H, s, $SiC(CH_3)_3$], 1.24-1.39 (10 H, m, 5 × CH_2), 1.53 (2 H, m, 7-H_2), 1.81 and 1.88 (each 1 H, m, 2-H), 2.08-2.23 (2 H, m, 6-H_2), 3.09 (1 H, br. s, OH), 3.86 and 3.96 (each 1 H, m, 1-H), 4.20 (1 H, m, 3-H), 5.25 and 5.48 (each 1 H, s, 5-CH), 7.37-7.49 (6 H, m, ArH) and 7.63-7.73 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 14.1, 19.1, 22.7, 26.8, 27.8, 29.3, 29.4(2), 30.5, 31.7, 31.9, 61.9, 71.3 (t, $^2J_{C\text{-}F}$ 30.7), 115.4 (t, $^3J_{C\text{-}F}$ 9.1), 121.4 (dd, $^1J_{C\text{-}F}$ 248.4, 245.7), 127.8, 129.9, 132.9, 133.0, 135.5(2) and 143.0 (t, $^2J_{C\text{-}F}$ 22.7); δ_F (377 MHz, $CDCl_3$) −114.15 and −110.23 (both d, $^2J_{F\text{-}F}$ 247.3); *m/z* (APCI) 503.3 ($M^+ + 1$, 100%).

1-*tert*-Butyldiphenylsilyloxy-4,4-difluorohex-5-en-3-one (58). *N*-Methylmorpholine-*N*-oxide (52 mg, 0.446 mmol) and TPAP (5 mg, 0.015 mmol) were added to the alcohol **40** (0.116 g, 0.297 mmol) and 4Å molecular sieves (0.168 g) in dry DCM (2.0 mL) and the mixture stirred for 16 h then concentrated under reduced pressure. Chromatography of the residue (light petroleum to 2:98 ether:light petroleum) gave the *title compound* **58** (90 mg, 0.23 mmol, 78%) as a colourless oil, R_f = 0.43 (10:90 ether:light petroleum) (Found: M^+ + Na, 411.1568. $C_{22}H_{26}O_2F_2SiNa$ requires M, 411.1568); ν_{max}/cm^{-1} 2957, 2931, 2857, 1746, 1427, 1107, 998, 956, 821 and 738; δ_H (500 MHz, $CDCl_3$) 1.05 [9 H, s, $SiC(CH_3)_3$], 2.92 (2 H, t, *J* 6.2, 2-H_2), 4.00 (2 H, t, *J* 6.2, 1-H_2), 5.66 (1 H, d, *J* 11.0, 6-H), 5.85 (1 H, dt, *J* 17.4, 2.5, 6-H'), 6.01 (1 H, m, 5-H), 7.39-7.48 (6 H, m, ArH) and 7.67-7.71 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 26.7, 39.4, 58.2, 114.3 (t, $^1J_{C\text{-}F}$ 251.2), 123.1 (t, $^3J_{C\text{-}F}$ 9.6), 127.7, 128.3 (t, $^2J_{C\text{-}F}$ 25.1), 129.8, 133.2, 135.5 and 198.2 (t, $^2J_{C\text{-}F}$ 32.4); δ_F (471 MHz, $CDCl_3$) −108.32; *m/z* (ES^+) 427 ($M^+ + 39$, 25%), 411 ($M^+ + 23$, 15) and 102 (100).

Methyl (*E*)- and (*Z*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluorohexa-2,5-dienoate (59) and (60). Methoxycarbonylmethylene(triphenyl)phosphorane (0.28 g, 0.844 mmol) was added to the ketone **58** (0.27 g, 0.703 mmol) in dry toluene (2.5 mL) and the mixture heated at 70 °C for 6 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 0.5:99.5 ether:light petroleum) gave the *title compound* **59** (0.26 g, 0.59 mmol, 84%) as a colourless oil, R_f = 0.38 (10:90 ether:light petroleum) (Found: M^+ + Na, 467.1841. $C_{25}H_{30}O_3F_2SiNa$ requires M, 467.1824); ν_{max}/cm^{-1} 2953, 2931, 2857, 1728, 1428, 1258, 1199, 1178, 1106, 1089, 981, 822 and 739; δ_H (400 MHz, $CDCl_3$) 1.05 [9 H, s, $SiC(CH_3)_3$], 2.99 (2 H, t, *J* 6.8, 1'-H_2), 3.70 (3 H, s, OCH_3), 3.81 (2 H, t, *J* 6.8, 2'-H_2), 5.45 (1 H, d, *J* 10.8, 6-H), 5.63 (1 H, dt, *J* 17.4, 2.2, 6-H'), 5.76-5.90 (1 H, m, 5-H), 6.21 (1 H, s, 2-H), 7.37-7.46 (6 H, m, ArH) and 7.66-7.71 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 26.8, 30.5 (t, $^3J_{C\text{-}F}$ 1.5), 51.5, 62.4, 118.7 (t, $^1J_{C\text{-}F}$ 243.1), 120.9 (t, $^3J_{C\text{-}F}$ 9.6), 121.2 (t, $^3J_{C\text{-}F}$ 8.8), 127.6, 129.6, 131.4 (t, $^2J_{C\text{-}F}$ 28.7), 133.7, 135.6, 149.4 (t, $^2J_{C\text{-}F}$ 25.0) and 165.6; δ_F (471 MHz, $CDCl_3$) −100.52; *m/z* (ES^+) 467.3 ($M^+ + 23$, 100%). The second fraction was the *title compound* **60** (36 mg, 0.081 mmol, 11%) as a colourless oil, R_f = 0.27 (10:90 ether:light petroleum) (Found: M^+ + Na, 467.1836. $C_{25}H_{30}O_3F_2SiNa$ requires M, 467.1824); ν_{max}/cm^{-1} 2953, 2931, 2857, 1735, 1428, 1240, 1196,

1159, 1105, 997, 822 and 737; δ_H (400 MHz, $CDCl_3$) 1.06 [9 H, s, $SiC(CH_3)_3$], 2.41 (2 H, td, *J* 6.4, 0.8, 1'-H_2), 3.74 (3 H, s, OCH_3), 3.80 (2 H, t, *J* 6.4, 2'-H_2), 5.43 (1 H, d, *J* 11.3, 6-H), 5.63 (1 H, dt, *J* 17.3, 2.8, 6-H'), 5.98 (1 H, s, 2-H), 6.16 (1 H, m, 5-H), 7.36-7.47 (6 H, m, ArH) and 7.63-7.69 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 26.8, 34.6 (t, $^3J_{C\text{-}F}$ 3.7), 51.8, 61.8, 118.7 (t, $^1J_{C\text{-}F}$ 239.9), 120.1 (t, $^3J_{C\text{-}F}$ 8.8), 122.9 (t, $^3J_{C\text{-}F}$ 5.1), 127.7, 129.7, 132.0 (t, $^2J_{C\text{-}F}$ 27.8), 133.4, 135.6, 142.8 (t, $^2J_{C\text{-}F}$ 27.0) and 166.2; δ_F (377 MHz, $CDCl_3$) –95.73; *m/z* (ES^+) 467.3 (M^+ + 23, 100%) and 462.4 (M^+ + 18, 85).

1-*tert*-Butyldiphenylsilyloxy-4,4-difluoro-5-methylenetridecan-3-one (61). Anhydrous DMSO (51 μL, 0.723 mmol) was added dropwise to oxalyl chloride (31 μL, 0.362 mmol) in dry DCM (1.6 mL) at –78 °C. After 30 min, the alcohol **57g** (91 mg, 0.18 mmol) in dry DCM (1.0 mL) was added. After a further 45 min, triethylamine (0.20 mL, 1.45 mmol) was added and the mixture was stirred at rt for 1 h. Saturated aqueous ammonium chloride (10 mL) and DCM (10 mL) were added and the aqueous phase was extracted into DCM (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0.25:99.75 ether:light petroleum) gave the *title compound* **61** (55 mg, 0.11 mmol, 61%) as a colourless oil, R_f = 0.53 (5:95 ether:light petroleum) (Found: M^+ + Na, 523.2809. $C_{30}H_{42}O_2F_2SiNa$ requires M, 523.2820); ν_{max}/cm^{-1} 2955, 2928, 2857, 1749, 1428, 1106, 927, 822 and 737; δ_H (500 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.7, 13-H_3), 1.03 [9 H, s, $SiC(CH_3)_3$], 1.22-1.34 (10 H, m, 5 × CH_2), 1.47 (2 H, m, 7-H_2), 2.08 (2 H, t, *J* 7.6, 6-H_2), 2.88 (2 H, t, *J* 6.0, 2-H_2), 3.97 (2 H, t, *J* 6.0, 1-H_2), 5.32 and 5.55 (each 1 H, s, 5-CH), 7.37-7.47 (6 H, m, ArH) and 7.65-7.70 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 19.1, 22.6, 26.7, 27.5, 29.2, 29.3, 29.4 (t, $^4J_{C\text{-}F}$ 2.2), 31.8, 39.3, 58.0, 116.1 (t, $^1J_{C\text{-}F}$ 251.6), 117.1 (t, $^3J_{C\text{-}F}$ 8.8), 127.7, 129.7, 133.2, 135.5, 140.8 (t, $^2J_{C\text{-}F}$ 21.9) and 198.3 (t, $^2J_{C\text{-}F}$ 31.4); δ_F (471 MHz, $CDCl_3$) –109.74; *m/z* (ES^+) 523.4 (M^+ + 23, 100%).

Methyl (*E*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluoro-5-methylenetridec-2-enoate (62). Methoxycarbonyl-methylidene(triphenyl)phosphorane (37 mg, 0.11 mmol) was added to the ketone **61** (32 mg, 0.064 mmol) in toluene (0.23 mL) and the mixture heated at 70 °C for 11 h. After concentration under reduced pressure, chromatography of the residue (0.25:99.75 ether:light petroleum) gave the *title compound* **62** (17 mg, 0.031 mmol, 48%) as a colourless oil, R_f = 0.23 (5:95 ether:light petroleum) (Found: M^+ + Na, 579.3080. $C_{33}H_{46}O_3F_2SiNa$ requires M, 579.3082); ν_{max}/cm^{-1} 2928, 2856, 1729, 1428, 1256, 1200, 1177, 1105 and 739; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 6.8, 13-H_3), 1.04 [9 H, s, $SiC(CH_3)_3$], 1.21-1.35 (10 H, m, 5 × CH_2), 1.42 (2 H, m, 7-H_2), 1.94 (2 H, t, *J* 7.3, 6-H_2), 2.94 (2 H, t, *J* 7.7, 1'-H_2), 3.70 (3 H, s, OCH_3), 3.76 (2 H, t, *J* 7.7, 2'-H_2), 5.17 and 5.40 (each 1 H, s, 5-CH), 6.22 (1 H, t, *J* 1.8, 2-H), 7.35-7.47 (6 H, m, ArH) and 7.66-7.72 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 14.1, 19.1, 22.6, 26.7, 27.5, 29.2(2), 29.4, 29.5, 30.7, 31.8, 51.5, 62.4, 115.9 (t, $^3J_{C\text{-}F}$ 8.1), 120.6 (t, $^1J_{C\text{-}F}$ 243.7), 121.3 (t, $^3J_{C\text{-}F}$ 9.0), 127.6, 129.5, 133.7, 135.6, 142.5 (t, $^2J_{C\text{-}F}$ 24.4), 148.9 (t, $^2J_{C\text{-}F}$ 25.3) and 165.6; δ_F (377 MHz, $CDCl_3$) –101.98; *m/z* (ES^+) 579.4 (M^+ + 23, 100%).

Ethyl 5-*tert*-butyldiphenylsilyloxy-2,2-difluoro-3-oxopentanoate (63). With rigorous exclusion of O_2, SmI_2 (0.1 M in THF, 48 mL, 48 mmol) was added to the aldehyde **39** (0.50 g, 1.6 mmol) and ethyl 2-bromo-2,2-difluoroacetate **11** (0.22 mL, 1.76 mmol) in dry THF (16 mL) and the yellow mixture was stirred at rt for 10 min. Aqueous hydrogen chloride (1 M, 50 mL) was added slowly followed by ether (50 mL). The aqueous phase was extracted with ether (3 × 50 mL) and the organic extracts were washed with saturated aqueous sodium thiosulfate (50 mL) then brine (250 mL) and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue (0.5:99.5 to 10:90 ether:light petroleum) gave ethyl 5-*tert*-butyldiphenylsilyloxy-2,2-difluoro-3-hydroxypentanoate (0.68 g, 1.57 mmol, 98%) as a colourless oil, R_f = 0.09 (10:90 ether:light petroleum) (Found: M^+ + Na, 459.1797. $C_{23}H_{30}O_4F_2SiNa$ requires M, 459.1779); ν_{max}/cm^{-1} 3476, 3071, 2959, 2931, 2888, 2858, 1759, 1472, 1446, 1307, 1206, 1106, 822 and 738; δ_H (400 MHz, $CDCl_3$) 1.06 [9 H, s, $SiC(CH_3)_3$], 1.39 (3 H, t, *J* 7.0, OCH_2CH_3), 1.87-1.95 (2 H, m, 4-H_2), 3.42 (1 H, br. s, 3-OH), 3.85-4.01 (2 H, m, 5-H_2), 4.39 (2 H, q, *J* 7.0, OCH_2CH_3), 4.44 (1 H, m, 3-H), 7.35-7.50 (6 H, m, ArH) and 7.61-7.75 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 13.9, 19.0, 26.8, 30.8, 61.7, 62.9, 70.9 (dd, $^2J_{C\text{-}F}$ 29.4, 24.8), 114.6 (dd, $^1J_{C\text{-}F}$ 262.6, 252.5), 127.8, 129.9(2), 132.7, 132.8, 135.5(2) and 163.6 (dd, $^2J_{C\text{-}F}$ 33.1, 31.2); δ_F (377 MHz, $CDCl_3$) –123.62 and –114.47 (both d, $^2J_{F\text{-}F}$ 261.2); *m/z* (ES^+) 459.3 (M^+ + 23, 90%) and 102 (100).

N-Methylmorpholine-*N*-oxide (83 mg, 0.71 mmol) and TPAP (8 mg, 0.024 mmol) were added to a suspension of this alcohol (0.21 g, 0.47 mmol) and 4Å molecular sieves (0.27 g) in DCM (2.7 mL) and the mixture stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 0.25:99.75 ether:light petroleum) gave the *title compound* **63** (0.13 g, 0.30 mmol, 63%) as a colourless oil, R_f = 0.29 (10:90 ether:light petroleum) (Found: M^+ + Na, 457.1619. $C_{23}H_{28}O_4F_2SiNa$ requires M, 457.1617); ν_{max}/cm^{-1} 3071, 2957, 2931, 2889, 2857, 1777, 1751, 1428, 1111, 822 and 739; δ_H (500 MHz, $CDCl_3$) 1.04 [9 H, s, $SiC(CH_3)_3$], 1.35 (3 H, t, *J* 7.2, OCH_2CH_3), 2.99 (2 H, t, *J* 6.0, 4-H_2), 4.00 (2 H, t, *J* 6.0, 5-H_2), 4.37 (2 H, q, *J* 7.2, OCH_2CH_3), 7.38-7.48 (6 H, m, ArH) and 7.66-7.71 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.8, 19.1, 26.6, 39.6, 57.8, 63.7, 108.1 (t, $^1J_{C\text{-}F}$ 262.5), 127.7, 129.8, 133.1, 135.5, 161.2 (t, $^2J_{C\text{-}F}$ 30.6) and 195.5 (t, $^2J_{C\text{-}F}$ 28.4); δ_F (471 MHz, $CDCl_3$) –114.16; *m/z* (ES^+) 457.2 (M^+ + 23, 60%).

Methyl (*E*)- and (*Z*)-5-*tert*-butyldiphenylsilyloxy-3-(ethoxycarbonyldifluoromethyl)pent-2-enoate (64) and (65). Methoxycarbonylmethylidene(triphenyl)phosphorane (0.12 g, 0.36 mmol) was added to the ketone **63** (0.13 g, 0.30 mmol) in toluene (1.10 mL) and the mixture stirred at 90 °C for 16 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 2:98 ether:light petroleum) gave the *title compound* **64** (0.12 g, 0.24 mmol, 82%) as a colourless oil, R_f = 0.20 (10:90 ether:light petroleum) (Found: M^+ + Na, 513.1893. $C_{26}H_{32}O_5F_2SiNa$ requires M, 513.1885); ν_{max}/cm^{-1} 2955, 2932, 2858, 1769, 1731, 1279, 1262, 1201, 1181, 1109, 1065, 823 and 740; δ_H (400 MHz, $CDCl_3$) 1.04 [9 H, s, $SiC(CH_3)_3$], 1.29 (3 H, t, *J* 7.3, OCH_2CH_3), 3.06 (2 H, t, *J* 7.2, 4-H_2), 3.70 (3 H, s, OCH_3), 3.78 (2 H, t, *J* 7.2, 5-H_2),

4.26 (2 H, q, *J* 7.3, OC*H*$_2$CH$_3$), 6.33 (1 H, s, 2-H), 7.36-7.46 (6 H, m, ArH) and 7.66-7.70 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.8, 19.1, 26.7, 30.1 (t, $^3J_{C\text{-}F}$ 1.5), 51.6, 62.0, 63.4, 113.1 (t, $^1J_{C\text{-}F}$ 254.9), 123.3 (t, $^3J_{C\text{-}F}$ 8.8), 127.6, 129.6, 133.5, 135.5, 146.0 (t, $^2J_{C\text{-}F}$ 22.1), 162.9 (t, $^2J_{C\text{-}F}$ 33.9) and 165.0; δ_F (377 MHz, $CDCl_3$) −107.08; *m/z* (ES$^+$) 513.2 (M$^+$ + 23, 80%), 491.2 (M$^+$ + 1, 20) and 256.9 (100). The second fraction was the *title compound* **65** (17 mg, 0.035 mmol, 12%) as a colourless oil; δ_H (500 MHz, $CDCl_3$) 1.07 [9 H, s, SiC(CH_3)$_3$], 1.31 (3 H, t, *J* 7.0, OCH$_2$C*H*$_3$), 2.63 (2 H, t, *J* 6.4, 4-H$_2$), 3.72 (3 H, s, OCH_3), 3.86 (2 H, t, *J* 6.7, 5-H$_2$), 4.32 (2 H, q, *J* 7.3, OC*H*$_2$CH$_3$), 6.10 (1 H, s, 2-H), 7.37-7.47 (6 H, m, ArH) and 7.66-7.70 (4 H, m, ArH); δ_F (471 MHz, $CDCl_3$) −100.24.

Methyl (*E*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluoro-5,6-dihydroxyhex-2-enoate (66). Acetonitrile (0.71 mL) and ruthenium(III) chloride hydrate (16 mg, 0.062 mmol) were added to the alkene **59** (0.14 g, 0.31 mmol) in aqueous EtOAc (1:1, 1.42 mL). Sodium periodate (0.066 g, 0.31 mmol) was added in ten equal portions over 5 h and the mixture stirred for a further 30 min before saturated aqueous sodium thiosulfate (10 mL) and EtOAc (10 mL) were added. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:99 to 50:50 ether:light petroleum) gave recovered alkene **59** (61 mg, 44%) followed by the *title compound* **66** (65 mg, 0.14 mmol, 44%) as a colourless oil, R_f = 0.60 (ether) (Found: M$^+$ + Na, 501.1898. $C_{25}H_{32}O_5F_2SiNa$ requires M, 501.1885); ν_{max}/cm^{-1} 3401, 2952, 2932, 2889, 2857, 1727, 1428, 1260, 1200, 1105, 1081, 1039, 822 and 738; δ_H (400 MHz, $CDCl_3$) 1.06 [9 H, s, SiC(CH_3)$_3$], 2.85 and 3.07 (each 1 H, dt, *J* 13.6, 6.3, 1'-H), 3.57 (1 H, br. s, OH), 3.69 (3 H, s, OCH_3), 3.82 (2 H, m, 6-H$_2$), 3.91 (2 H, t, *J* 6.3, 2'-H$_2$), 4.00 (1 H, m, 5-H), 6.30 (1 H, d, *J* 2.3, 2-H), 7.37-7.48 (6 H, m, ArH) and 7.63-7.70 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 26.8, 30.3, 51.6, 60.6 (dd, $^3J_{C\text{-}F}$ 4.4, 1.5), 63.4, 71.8 (dd, $^2J_{C\text{-}F}$ 32.4, 25.8), 120.6 (dd, $^1J_{C\text{-}F}$ 254.1, 247.5), 122.3 (dd, $^3J_{C\text{-}F}$ 11.1, 8.8), 127.8, 129.9, 132.8, 132.9, 135.5, 135.6, 149.0 (t, $^2J_{C\text{-}F}$ 22.1) and 165.4; δ_F (377 MHz, $CDCl_3$) −117.88 and −107.56 (each d, $^2J_{F\text{-}F}$ 249.0); *m/z* (ES$^+$) 501.3 (M$^+$ + 23, 100%).

Methyl (*E*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluoro-5-hydroxy-6,6-dimethylocta-2,7-dienoate (68). Solid sodium carbonate (39 mg, 0.37 mmol) and lead(IV) acetate (65 mg, 0.15 mmol) were added to the diol **66** (59 mg, 0.12 mmol) in DCM (1.2 mL). The mixture was stirred at rt for 30 min, filtered and concentrated under reduced pressure to give the aldehyde **67** that was azeotroped with benzene. 1-Bromo-3-methylbut-2-ene (0.14 mL, 1.23 mmol) was added to this aldehyde in THF (2.4 mL) and the solution was added to a suspension of zinc dust (80 mg, 1.23 mmol) and titanocene dichloride (3 mg, 0.012 mmol) in THF (2.45 mL) that had been pre-stirred for 5 min. The mixture was stirred for 2.5 h before aqueous hydrogen chloride (10%, 10 mL) and ether (10 mL were added. The aqueous phase was extracted with ether (3 × 30 mL) and the organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 ether:light petroleum) gave the *title compound* **68** (41 mg, 0.079 mmol, 65%) as a colourless oil, R_f = 0.40 (30:70 ether:light petroleum) (Found: M$^+$ + Na, 539.2392. $C_{29}H_{38}O_4F_2SiNa$ requires M, 539.2405); ν_{max}/cm^{-1} 3495, 3071, 2957, 2932, 2889, 2858, 1727, 1428, 1261, 1202, 1110, 1072, 916, 823 and 740; δ_H (400 MHz, $CDCl_3$) 1.05 [9 H, s, SiC(CH_3)$_3$], 1.16 (3 H, s, 6-CH_3), 1.18 (3 H, d, *J* 2.0, 6-CH_3), 2.80 (1 H, br. s, OH), 2.85 and 3.06 (each 1 H, dt, *J* 13.4, 6.8, 1'-H), 3.60 (1 H, d, *J* 23.4, 5-H), 3.68 (3 H, s, OCH_3), 3.82-3.90 (2 H, m, 2'-H$_2$), 5.04-5.11 (2 H, m, 8-H$_2$), 5.99 (1 H, ddq, *J* 17.4, 10.8, 1.2, 7-H), 6.23 (1 H, d, *J* 2.8, 2-H), 7.36-7.47 (6 H, m, ArH) and 7.65-7.70 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 19.1, 24.1 (t, $^4J_{C\text{-}F}$ 3.6), 24.2, 26.8, 30.9, 41.0, 51.5, 63.3, 76.5 (dd, $^2J_{C\text{-}F}$ 30.9, 26.4), 113.3, 121.4 (dd, $^3J_{C\text{-}F}$ 11.8, 8.2), 122.7 (dd, $^1J_{C\text{-}F}$ 259.3, 249.3), 127.7, 129.7(2), 133.1(2), 135.6(2), 144.1 (d, $^4J_{C\text{-}F}$ 1.8), 150.7 (t, $^2J_{C\text{-}F}$ 21.9) and 165.7; δ_F (377 MHz, $CDCl_3$) −115.62 and −99.51 (each d, $^2J_{F\text{-}F}$ 245.2); *m/z* (ES$^+$) 539.3 (M$^+$ + 23, 100%).

Methyl (*E*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluoro-6,6-dimethyl-5-oxo-octa-2,7-dienoate (69). *N*-Methylmorpholine-*N*-oxide (11 mg, 0.09 mmol) and TPAP (1 mg, 0.003 mmol) were added to a stirred suspension of the alcohol **68** (31 mg, 0.06 mmol) and 4Å molecular sieves (36 mg) in DCM (0.78 mL) and the mixture stirred at rt for 30 min then concentrated under reduced pressure. Chromatography of the residue (2:98 to 10:90 ether:light petroleum) gave the *title compound* **69** (27 mg, 0.053 mmol, 87%) as a colourless oil, R_f = 0.48 (10:90 ether:light petroleum) (Found: M$^+$ + Na, 537.2264. $C_{29}H_{36}O_4F_2SiNa$ requires M, 537.2249); ν_{max}/cm^{-1} 2932, 2857, 1729, 1428, 1261, 1201, 1109, 1039, 919, 823 and 740; δ_H (500 MHz, $CDCl_3$) 1.03 [9 H, s, SiC(CH_3)$_3$], 1.33 (6 H, s, 2 × 6-CH_3), 2.96 (2 H, t, *J* 7.3, 1'-H$_2$), 3.69 (3 H, s, OCH_3), 3.74 (1 H, t, *J* 7.3, 2'-H$_2$), 5.15 (1 H, d, *J* 17.4, 8-H), 5.19 (1 H, d, *J* 10.8, 8-H'), 5.95 (1 H, ddt, *J* 17.4, 10.8, 1.0, 7-H), 6.18 (1 H, t, *J* 1.6, 2-H), 7.36-7.45 (6 H, m, ArH) and 7.65-7.69 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 19.1, 24.0 (t, $^4J_{C\text{-}F}$ 1.8), 26.7, 30.5, 49.7, 51.6, 62.1, 116.1, 116.7 (t, $^1J_{C\text{-}F}$ 257.5), 123.3 (t, $^3J_{C\text{-}F}$ 9.9), 127.6, 129.5, 133.6, 135.6, 139.7, 146.7 (t, $^2J_{C\text{-}F}$ 21.7), 165.0 and 200.5 (t, $^2J_{C\text{-}F}$ 28.9); δ_F (471 MHz, $CDCl_3$) −102.04; *m/z* (ES$^+$) 537 (M$^+$ + 23, 100%), 437 (20) and 259 (80).

3,3-Difluoro-2-hydroxy-2-(3-methylbut-1-en-3-yl)-4-[(*E*)-methoxycarbonylmethylene]tetrahydro-4*H*-pyran (70). Hydrogen fluoride.pyridine complex (70% HF, 0.2 mL) was added rapidly to the ketone **69** (34 mg, 0.066 mmol) and pyridine (0.39 mL) in THF (3.9 mL) at 0 °C and the mixture stirred for 2.5 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was stirred at rt for 1 h. After the addition of EtOAc (10 mL), the aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 ether:light petroleum) gave the *title compound* **70** (15 mg, 0.054 mmol, 82%) as a colourless oil which solidified on cooling, R_f = 0.31 (30:70 ether:light petroleum), m.p. 54-56 °C (Found: C, 56.61; H, 6.64. $C_{13}H_{18}O_4F_2$ requires C, 56.50; H, 6.60%; Found: M$^+$ + Na, 299.1071. $C_{13}H_{18}O_4F_2Na$ requires M, 299.1071); ν_{max}/cm^{-1} 3515, 2956, 2918, 2850, 1729, 1127 and 1061: δ_H (400 MHz, benzene-d_6) 1.28 (3 H, d, *J* 4.0, 3'-CH_3 or 4'-H$_3$), 1.37 (3 H, d, *J* 2.5, 4'-H$_3$ or 3'-CH_3), 2.41 (1 H, dd, *J* 13.4, 6.6, 5-H), 2.46 (1 H, d, *J* 3.5, OH), 3.24 (3 H, s, OCH_3), 3.41 (1 H, dd, *J* 11.1, 6.6,

5-H'), 3.76 and 3.97 (each 1 H, m, 6-H), 4.82-4.93 (2 H, m, 1'-H_2), 6.06 (1 H, dd, *J* 17.9, 10.6, 2'-H) and 6.44 (1 H, dd, *J* 4.0, 2.3, 4-CH); δ_C (125 MHz, benzene-d_6) 21.8 and 24.1 (each d, $^4J_{C\text{-}F}$ 6.3), 28.6 (d, $^3J_{C\text{-}F}$ 2.7), 46.5, 51.3, 60.5, 99.1 (dd, $^2J_{C\text{-}F}$ 30.1, 24.4), 115.4, 117.4 (dd, $^3J_{C\text{-}F}$ 13.5, 6.3), 118.4 (dd, $^1J_{C\text{-}F}$ 263.6, 243.7), 144.5, 148.8 (dd, $^2J_{C\text{-}F}$ 20.8, 18.1) and 166.3; δ_F (377 MHz, benzene-d_6) −119.61 and −105.38 (each d, $^2J_{F\text{-}F}$ 241.5); *m/z* (ES^+) 299.1 (M^+ + 23, 100%).

X-Ray structure determination for (2*RS*,4*RS*)-2-*tert*-butyl-3,3-difluoro-2,4-dihydroxytetrahydro-2*H*-pyran (44). Single crystal X-ray diffraction data were collected on a Bruker Prospector CCD diffractometer at 100 K using graphite monochromated Cu radiation (**λ** = 1.54178 Å). The data were reduced by SAINTPLUS; XPREP was used to determine the space group. The crystal structure was solved by direct methods using SHELXS97 and refined by the full-matrix least-squares method on F^2 using SHELXL97. Crystal data: $C_9H_{16}F_2O_3$, M = 210.22; monoclinic, P2(1)/c, a = 11.2814(2), b = 16.1595(2), c = 12.1971 (2) Å, V = 2043.55(6) $Å^3$, Z = 8, 9593 reflections measured, 3933 independent reflections (R_{int} = 0.0207) > 2σ(I) (R_1 = 0.0358 and wR_2 = 0.0952); CCDC number 1016876.