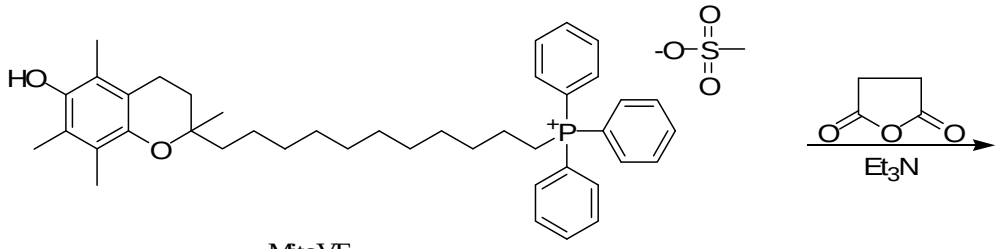
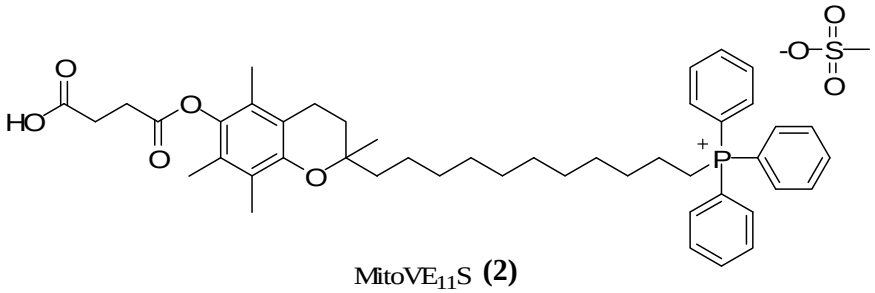
Synthesis of VE Analogs

1. Synthesis of *rac*-MitoVE$_{11}$S (**2**)

The synthetic route used MitoVE$_{11}$ as a precursor (VJAJ and RAJS, manuscript in preparation) as shown below.

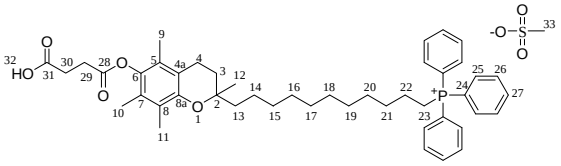


MitoVE$_{11}$



MitoVE$_{11}$S **(2)**

{11-[6-(3-Carboxy-propionyloxy)-2,5,7,8-tetramethyl-chroman-2-yl]-undecyl}triphenyl-phosphonium methanesulfonate (MitoVE$_{11}$S) **(2)**



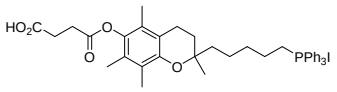
A solution of {11-[6-(3-carboxy-propionyloxy)-2,5,7,8-tetramethyl-chroman-2-yl]-undecyl}triphenylphosphonium methanesulfonate[1] (30.3 mg, 42.3 μmol) and succinic anhydride (6.35 mg, 63.5 μmol) and Et_3N (18 μl, 127 μmol) in CH_2Cl_2 (0.20 ml) was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 (5 ml) and this was washed with aqueous methane sulfonic acid (10%, 3 × 5 ml), dried over $MgSO_4$, filtered and concentrated to give an orange oil. The crude product was purified by column chromatography on silica gel. Elution with EtOH:CH_2Cl_2 (1:39) gave **3** as a pale yellow oil which, after freeze drying, was a pale yellow solid (20.6 mg, 25.2 μmol, 60%). MS (+ve ESI) m/z calcd. for $C_{46}H_{58}O_5P^+$: 721.4016, found: 721.3987; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.09 – 1.30 (12H, m, **H15** – **H20**) 1.22 (3H, s, **H12**), 1.35 (2H, quin, *J*=7.3 Hz, **H14**), 1.40 – 1.64

(6H, m, **H13**, **H21**, **H22**), 1.68 – 1.84 (2H, m, **H3**), 1.93 (3H, s, **H9**), 1.95 (3H, s, **H10**), 2.03 (3H, s, **H11**), 2.54 (2H, t, *J*=6.5 Hz, **H4**), 2.74 (3H, s, **H33**), 2.77 (3H, s, **H29**), 2.84 (3H, s, **H30**), 3.43 (2H, m, **H23**), 7.66 – 7.72 (6H, m, **H26**), 7.74 – 7.82 (12H, m, **H25**, **H27**); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 11.86 (1C, s, **C11**) 12.12 (1C, s, **C9**), 12.99 (1C, s, **C10**), 20.64 (1C, s, **C4**), 21.99 (1C, d, *J*=50.0 Hz, **C23**), 22.59 (1C, s (br), **C22**), 23.29 (1C, s, **C14**) 24.53 (1C, s, **C12**), 29.16, 29.30, 29.44, 29.73 (8C, 4 × s (br), **C15** – **C20**), 30.37 (1C, d, *J*=15.6 Hz, **C21**), 31.28 (1C, s, **C3**), 38.50 (1C, s, **C13**), 39.49 (1C, s, **H29**), 75.02 (1C, s, **C2**), 117.40 (1C, s, **C4a**), 118.46 (1C, d, *J*=85.3 Hz, **C21**), 122.81 (1C, s, **C7**), 125.15 (1C, s, **C5**), 126.84 (1C, s, **C8**), 140.62 (1C, s, **C6**), 149.30 (1C, s, **C8a**), 130.56 (1C, d, *J*=12.25 Hz, **C26**), 133.60 (1C, d, *J*=9.9 Hz, **C25**), 135.07 (1C, d, *J*=2.9 Hz, **C27**), 171.22 (1C, s, **C28**), 174.32 (1C, s, **C31**) ^{31}P NMR (121 MHz, $CDCl_3$) δ (ppm) 25.5.

2. Preparation of short-chain homologs of *rac*-Mito$VE_{11}S$

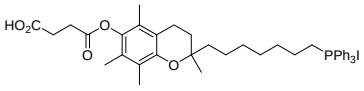
The detailed protocol for preparation of these compounds will be published elsewhere.

{5-[6-(3-carboxypropionyloxy)-2,5,7,8-tetramethylchroman-2-yl]-pentyl}triphenylphosphonium iodide (MitoVE_5S) **(5)**



Oil. Yield : 76%. MS (+ve ESI) m/z calcd. for $C_{40}H_{46}O_5P^+$: 637.3077, found: 637.3068; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.83-7.71 (m, 9H), 7.71-7.61 (m, 6H), 3.61-3.45 (m, 2H), 2.88-2.58 (m, 4H), 2.58-2.44 (m, 2H), 1.96 (s, 3H), 1.92 (s, 3H), 1.89 (s, 3H), 1.74-1.32 (m, 10H), 1.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 171.6, 171.2, 149.4, 140.9, 135.5, 133.9, 130.8, 127.1, 125.4, 122.9, 118.7, 118.0, 117.6, 75.0, 31.4, 31.0, 30.9, 29.7, 29.5, 29.2, 24.3, 23.2, 22.7, 20.8, 13.2, 12.3, 12.1.

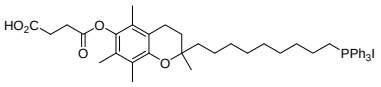
{7-[6-(3-carboxypropionyloxy)-2,5,7,8-tetramethylchroman-2-yl]-heptyl}triphenylphosphonium iodide (MitoVE_7S) **(4)**



Oil. Yield : 64%. MS (+ve ESI) m/z calcd. for $C_{42}H_{50}O_5P^+$: 665.3390, found: 665.3377; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.81-7.72 (m, 9H), 7.71-7.65 (m, 6H), 3.60-3,44 (m, 2H), 2.96-2.85 (m, 4H), 2.54-2.48 (m, 2H), 2.00 (s, 3H), 1.94 (s, 3H), 1.91 (s, 3H), 1.78-1.65 (m, 2H), 1.63-1.52 (m, 4H),

1.52-1.36 (m, 2H), 1.36-1.22 (m, 6H), 1.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 171.4, 149.6, 140.8, 135.5, 133.9, 130.9, 127.0, 125.4, 123.1, 118.8, 118.1, 117.7, 75.3, 39.5, 31.4, 30.6, 29.8, 29.6, 29.2, 24.4, 23.7, 23.4, 23.0, 22.8, 20.9, 13.2, 12.4, 12.1.

{9-[6-(3-carboxypropionyloxy)-2,5,7,8-tetramethylchroman-2-yl]-nonyl}triphenylphosphonium iodide (MitoVE$_9$S) **(3)**



Oil. Yield : 60%. MS (+ve ESI) m/z calcd. for $C_{44}H_{54}O_5P^+$: 693.3703, found: 693.3675; ^{1}H NMR (500 MHz, MeOD) δ 7.89-7.70 (m, 15H), 3.46-3.39 (m, 2H), 2.87 (t, 2H, J=7 Hz), 2.67 (t, 2H, J=6.5 Hz), 2.58 (t, 2H, J=6.5 Hz), 2.03 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.82-1.70 (m, 2H), 1.70-1.60 (m, 2H), 1.60-1.45 (m, 4H), 1.45-1.36 (m, 2H), 1.34-1.22 (m, 8H), 1.20 (s, 3H). ^{13}C NMR (125 MHz, MeOD) δ 176.1, 173.2, 150.4, 142.0, 136.2, 134.8, 131.5, 127.9, 126.3, 123.6, 120.2. 119.5, 118.7, 76.1, 40.2, 32.4, 31.5, 31.4, 31.0, 30.3, 30.1, 29.8, 24.5, 24.2, 23.5, 23.0, 22.6, 21.5, 13.2, 12.3, 12.1.

3. Preparation of MitoVE$_{11}$S enantiomers

The two individual enantiomers *S*-MitoVE$_{11}$S (6) and *R*-MitoVE$_{11}$S (7) were prepared in a similar manner to *rac*-MitoVE$_{11}$S (**3**), starting from (*R*)-(+)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid and (*S*)-(-)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, respectively. These two non-racemic precursors were purchased from MP Biomedicals and Aldrich, respectively. Note that we obtained the (*S*)-MitoVE$_{11}$S from the(*R*)-chroman, and we obtained the (*R*)-MitoVE$_{11}$S from the (*S*)-chroman, the reason for this being that the Cahn-Ingold-Prelego priority of the groups changes when the long chain is attached to the chroman precursor. Full details of the synthesis will be published elsewhere.