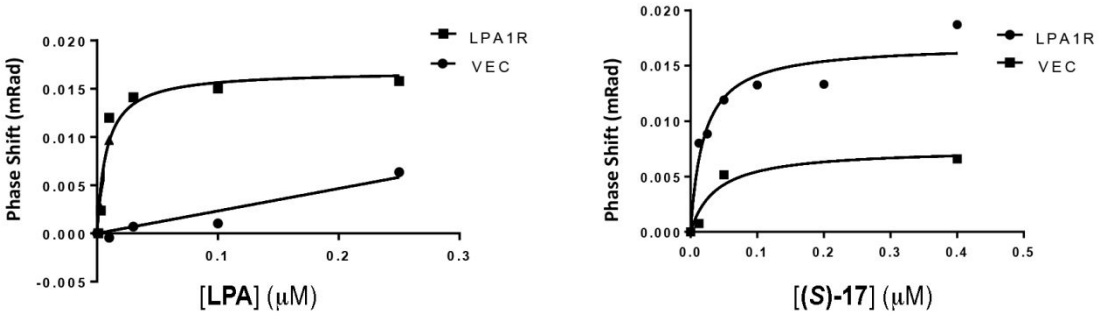
Supporting Information

A novel agonist of the type 1 lysophosphatidic acid receptor (LPA_1), UCM-05194, shows efficacy in neuropathic pain amelioration

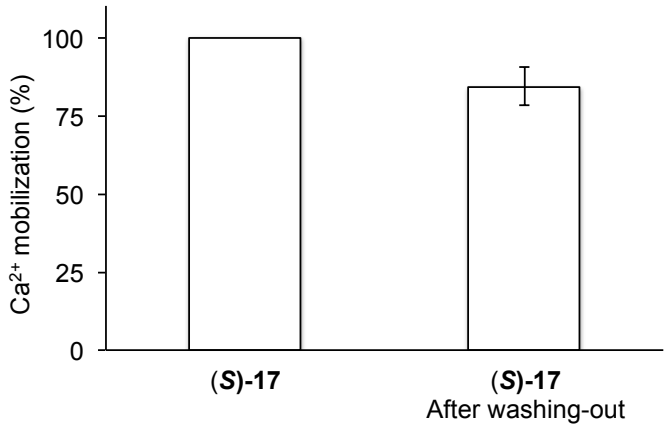
Inés González-Gil, Debora Zian, Henar Vázquez-Villa, Gloria Hernández-Torres, R. Fernando Martínez, Nora Khiar, Richard Rivera, Yasuyuki Kihara, Isabel Devesa, Sakthikumar Mathivanan, Cristina Rosell del Valle, Emma Zambrana-Infantes, María Puigdomenech, Giovanni Cincilla, Melchor Sánchez-Martínez, Fernando Rodríguez de Fonseca, Antonio V. Ferrer-Montiel, Jerold Chun, Rubén López-Vales, María L. López-Rodríguez and Silvia Ortega-Gutiérrez

Table of Contents

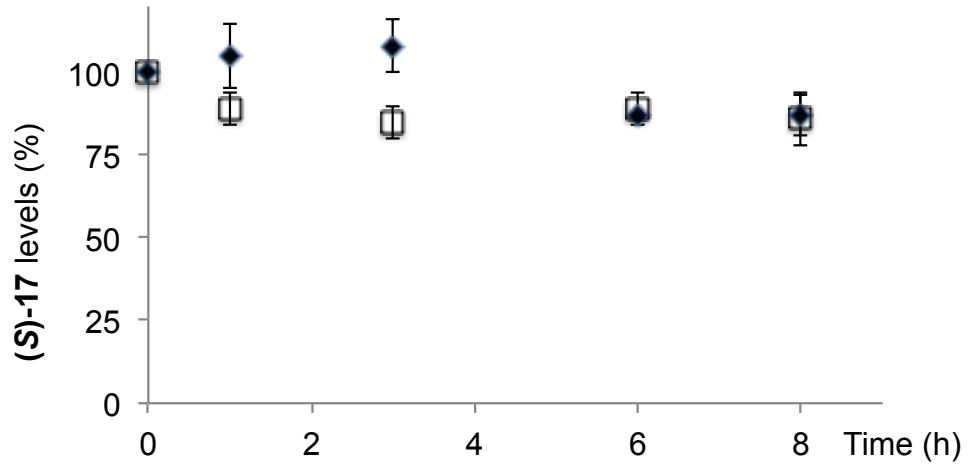
1. Supporting Figures



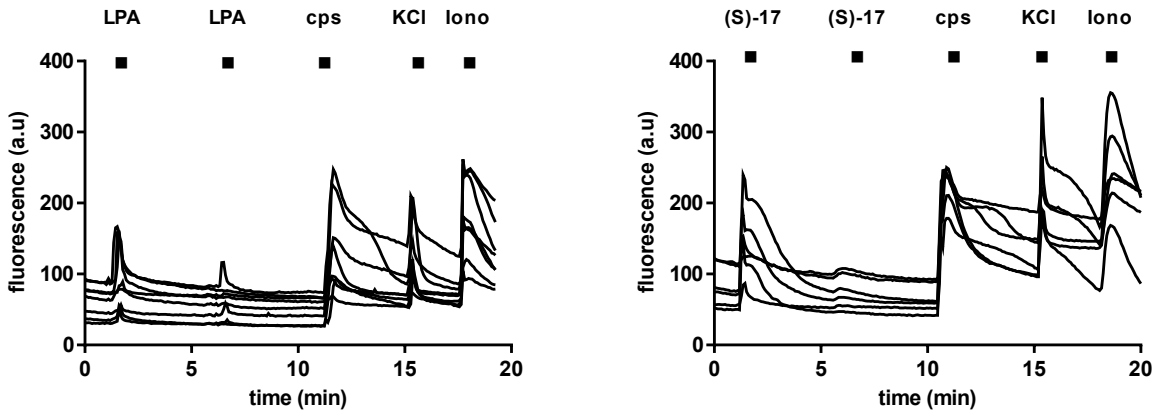
Supporting Figure S1. Representative plots of BSI signal versus ligand concentration for the determination of affinity constant. Each data point represents the average of at least four independent measurements. Membranes from cells transfected with the empty plasmid -without any receptor (VEC)- were used as negative control.



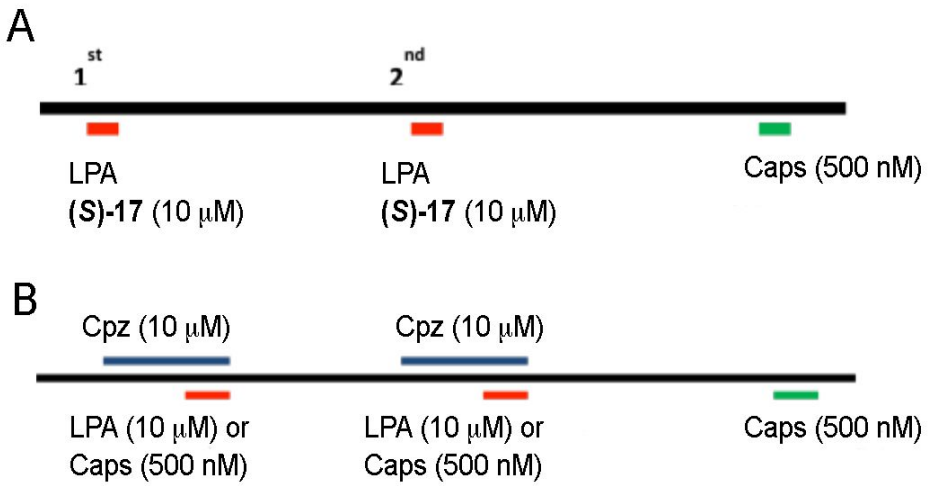
Supporting Figure S2. Changes in intracellular calcium levels were measured by using Fluo-4 NW (Invitrogen). RH7777 hepatoma cells stably expressing the LPA_1 receptor were plated at a density of 50000 cells/well and cultured overnight. The culture medium was then replaced with Fluo-4 NW dye loading solution containing 2.5 μM of probenecid and incubated for 30 minutes at 37 ºC followed by an additional 30 minutes at rt. After addition of the compound, fluorescence changes were registered in a FluoStar Optima instrument (BMG Labtech) at 525 nm using an excitation wavelength of 494 nm. For assessing covalent binding, after the initial stimulation with compound **(*S*)-17**, media was removed, cells washed with buffer, and, after 30 minutes, fresh compound was added and Ca^{2+} mobilization measured as described above. Data are expressed as mean ± SEM and correspond to two independent experiments carried out in triplicate.



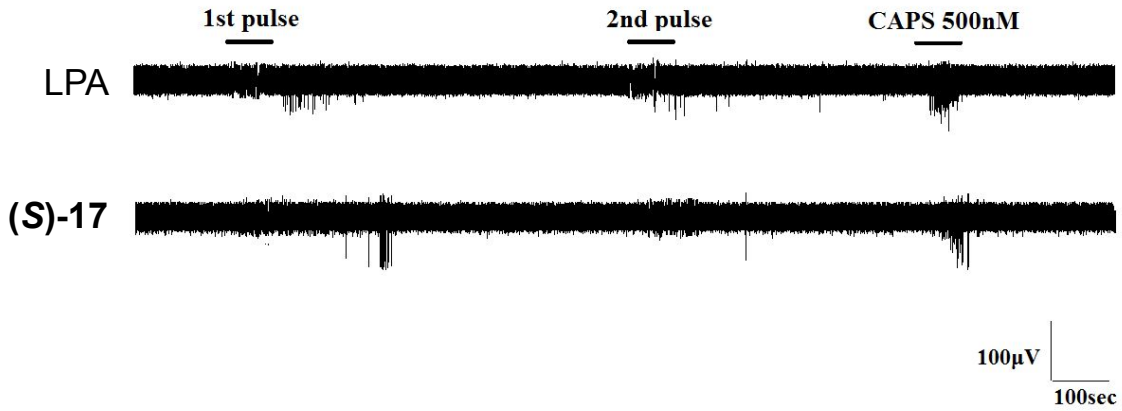
Supporting Figure S3. Stability of **(*S*)-17** in PBS (black diamonds) and in culture media at 37 ºC (white squares). Remaining compound at each time point was quantified by HPLC-MS (SIM mode) using the peak area integration normalized with an internal standard. Data are expressed as mean±SEM and correspond to two independent experiments carried out in duplicate.



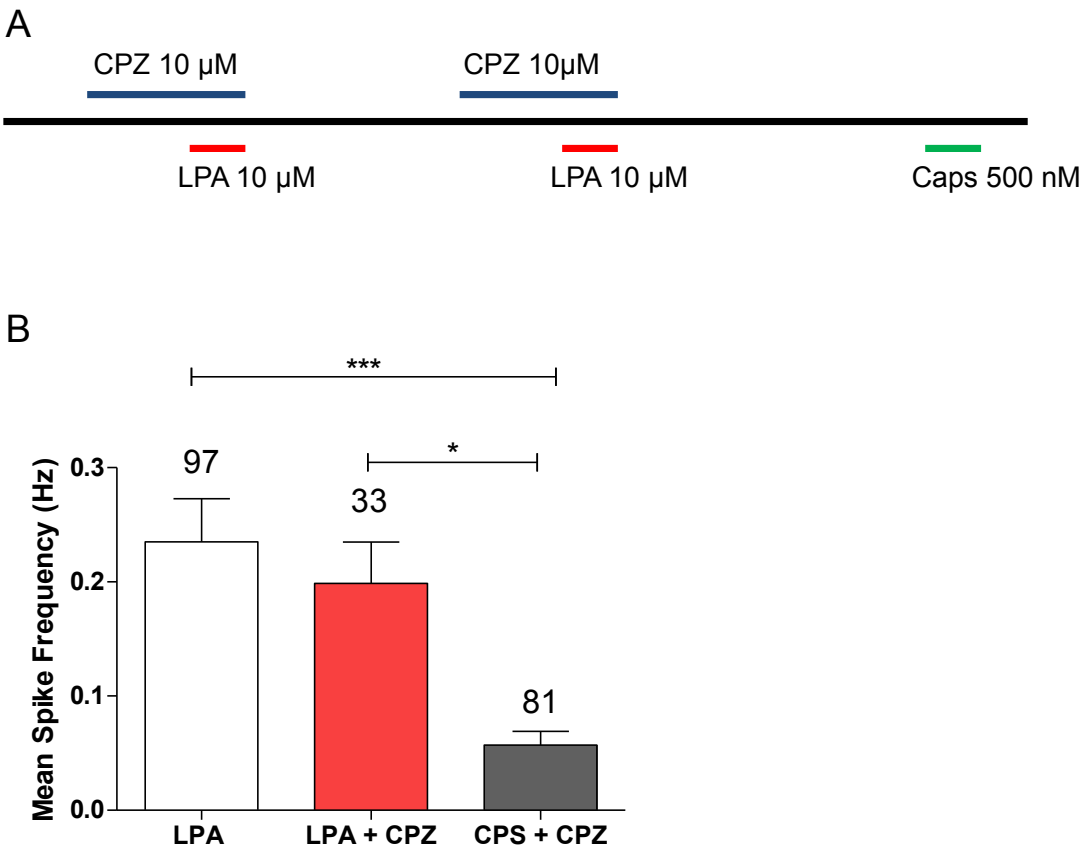
Supporting Figure S4. Representative calcium microfluorography recordings on neonatal rat cultures. LPA (A) and **(*S*)-17** (B) were applied in two repetitive 10 s-pulses at 10 μM. TRPV1 channel activity evoked with 10 s-application of capsaicin (cps) at 1 μM. 10 s pulse of 40 mM KCl applied to distinguish neuronal viability. Ionomycin (iono) was used at 5 μM to determine maximal calcium influx detection.



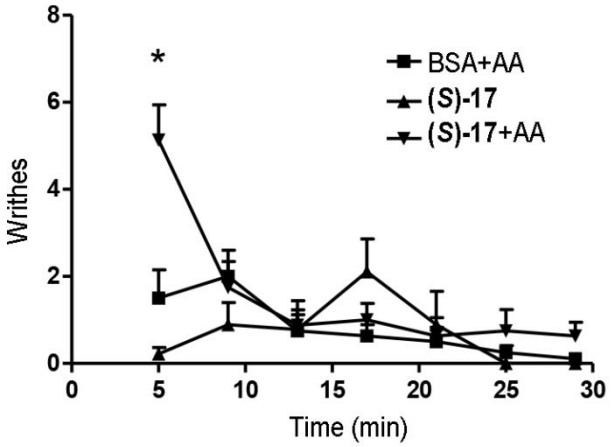
Supporting Figure S5. Experimental protocol for microelectrode array (MEA). (A) LPA and **(*S*)-17** at 10 μM concentration were applied (15 secs) in neonatal rat cultured DRGs with 4 minutes time interval between each pulse. The evoked neuronal spikes were measured using MEA technique. (B) For experiments with capsazepine (Cpz), neurons were exposed to 10 μM Cpz for 1 minute followed by co-application with LPA 10 μM or capsaicin (Caps) 500 nM. In both protocols, a pulse of capsaicin 500 nM was applied at the end to identify capsaicin sensitive neurons.



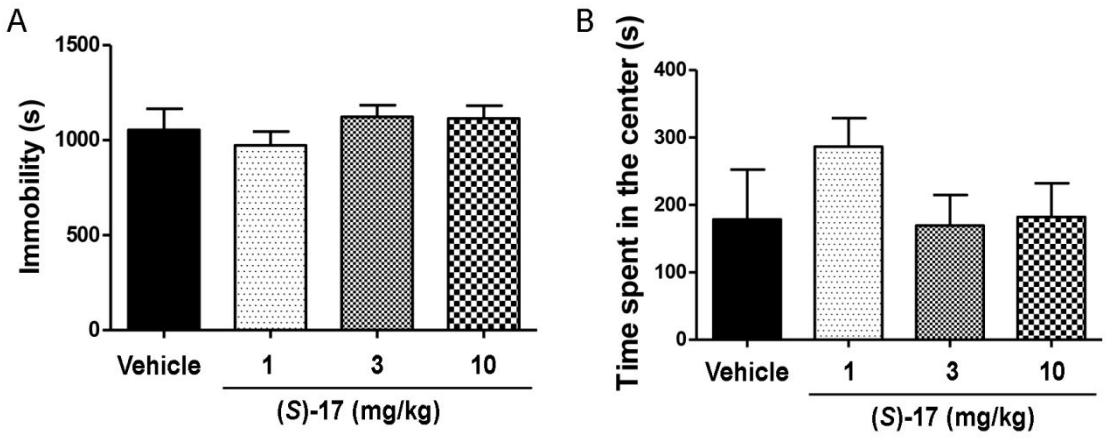
Supporting Figure S6. Representative MEA recordings of LPA (10 μM), (*S*)-17 (10 μM), and capsaicin (500 nM) induced action potentials. LPA and **(*S*)-17** (15 sec) application at 10 μM concentration on neonatal rat DRG neurons induced few traceable neuronal spikes which is followed by 15 sec capsaicin application at 500 nM concentration.



Supporting Figure S7. Comparison of neuronal groups treated with LPA, capsazepine (CPZ) and capsaicin (CPS). (A) Schematic representation of the used protocol. LPA at 10 µM concentration was applied (15 secs) in neonatal rat cultured DRGs with 4 minutes time interval between each pulses and the evoked neuronal spikes were measured using MEA technique. Capsaicin (500 nM) was applied at the end of the protocol to measure the capsaicin sensitivity of the neurons exposed to LPA. For experiments with capsazepine, neurons were exposed to 10 µM CPZ for 1 minute followed by co application with LPA 10µM. (B) Neuronal groups treated with 10 µM LPA, 10 µM LPA + 10 µM CPZ, and 500 nM CPS + 10 µM CPZ only first exposure (1st pulse) mediated neuronal firing activity on neonatal rat DRG neurons are represented as mean spike frequency (Hz). Responses to LPA were similar in activity compared to LPA+CPZ, whereas both groups were significantly different when compared to CPS+CPZ treated groups. Data are expressed as mean ± SEM. Numbers above the error bars denotes number of electrodes responded. Number of cultures ≥2. One way ANOVA, Bonferroni post hoc test.



Supporting Figure S8. Acute administration of (*S*)-17 increased the acetic acid-induced writhing responses in the first 5 minutes. Mice received an i.p. injection of vehicle (3% BSA) or **(*S*)-17** (10 mg/kg) 60 minutes prior to the administration of the 0.6% acetic-acid solution (AA). Data show mean values ± SEM. * $p<0.05$ to BSA+AA group (one-way ANOVA).



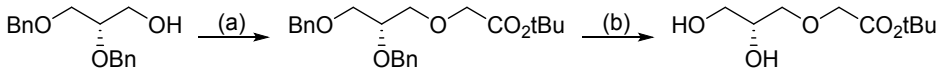
Supporting Figure S9. Compound (*S*)-17 does not alter motor activity in the open field test. There was no difference in immobility time (A) and the spent time in the center of the arena (B) between the doses of **(*S*)-17** and vehicle solution (BSA 3%). (n=6-4 per group).

2. Supporting Table S1. Agonist activities of compounds at LPA_1, LPA_2 and LPA_3 receptors

Cpd.	LPA_1R		LPA_2R		LPA_3R	
	E_{max} (%)[a]	EC_{50} (μM)[b]	E_{max} (%)	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)
6	33 ± 5	1.7 ± 0.2	N.E.[c]	-	N.E.	-
7	74 ± 14	6 ± 1	N.E.	-	N.E.	-
12	127 ± 1	2.8 ± 0.1	42 ± 5	8.1 ± 0.8	26.6 ± 0.4	11 ± 3
13	205 ± 9	0.45 ± 0.01	N.E.	-	96 ± 22	22 ± 5
14	202 ± 1	2.1 ± 0.3	N.E.	-	84 ± 6	16 ± 3
15	88 ± 2	3.6 ± 0.2	N.E.	-	34 ± 3	14 ± 2
(*S*)-17	118 ± 14	0.24 ± 0.09	N.E.	-	N.E.	-
20	74 ± 4	2.1 ± 0.3	59 ± 2	12 ± 2	N.E.	-
21	112 ± 3	0.5 ± 0.1	74 ± 6	5.3 ± 0.6	25 ± 3	15 ± 4
22	135 ± 31	3.2 ± 0.5	N.E.	-	N.E.	-
25	127 ± 9	3.3 ± 0.6	N.E.	-	N.E.	-
26	37 ± 1	19 ± 2	N.E.	-	N.E.	-
69	43 ± 6	1.4 ± 0.6	81 ± 1	10.8 ± 0.8	33 ± 6	10 ± 3
79	39 ± 3	3.2 ± 0.4	67 ± 8	4.9 ± 0.2	N.E.	-
85	26 ± 1	5 ± 1	88 ± 13	15 ± 2	70 ± 16	8 ± 1

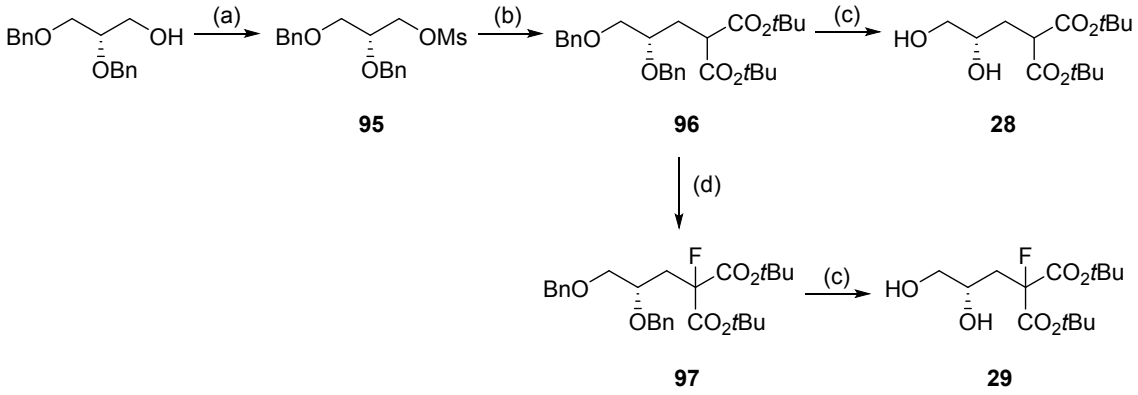
[a]E_{max} = maximal efficacy of the drug/maximal efficacy of LPA, expressed as the percentage. [b]For E_{max} > 30%, EC_{50} values are expressed as mean ± s.e.m, from a minimum of two independent experiments, performed in triplicate. [c]N.E., no effect was observed at the highest concentration of compound tested (10 μM).

3. Synthetic Schemes S1-S16



94 **27**

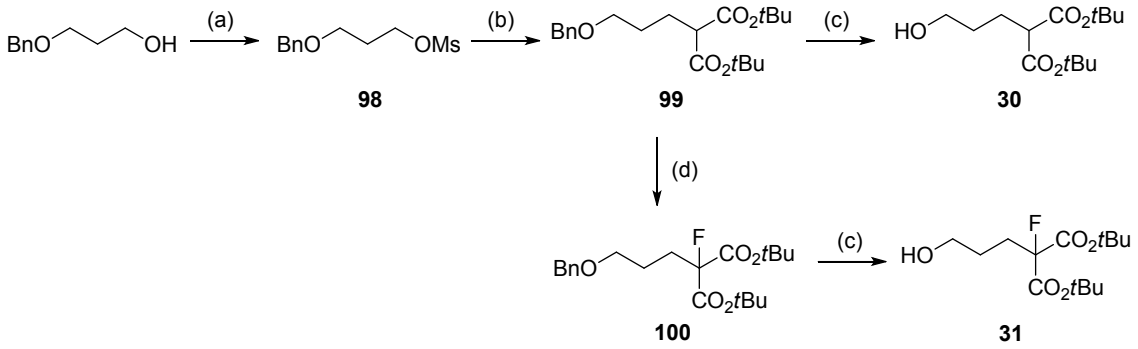
Scheme S1. Reagents and conditions: (a) *tert*-Butyl bromoacetate, NaH, TBAI, THF, 0ºC to 50ºC, 16 h, 22%; (b) H_2, 10% Pd/C, EtOH, 60ºC, 95%.



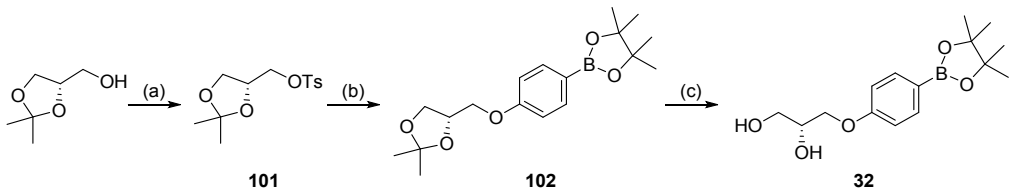
95 **96** **28**

97 **29**

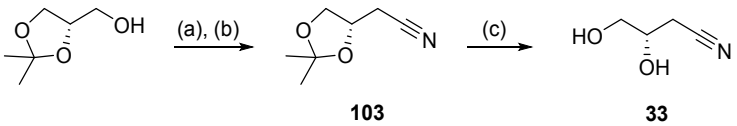
Scheme S2. Reagents and conditions: (a) Mesyl chloride, Et_3N, DCM, 0ºC to rt, 1 h, 80%; (b) di-*tert*-butyl malonate, NaH, NaI, DMF:THF, 0ºC to 80ºC, 17 h, 76%; (c) H_2, 10% Pd/C, EtOH, 60ºC, 99%; (d) Selectfluor®, NaH, DMF:THF, 0ºC to rt, 48 h, 99%.



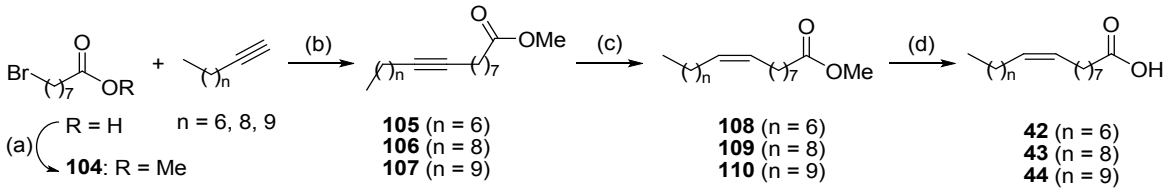
Scheme S3. Reagents and conditions: (a) Mesyl chloride, Et_3N, DCM, 0ºC to rt, 1 h, 99%; (b) di-*tert*-butyl malonate, NaH, NaI, DMF:THF, 0ºC to 80ºC, 17 h, 66%; (c) H_2, 10% Pd/C, EtOH, 60ºC, 95%. (d) Selectfluor®, NaH, DMF:THF, 0ºC to rt, 48 h, 99%.



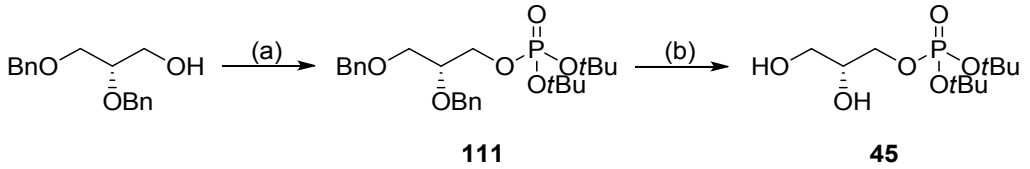
Scheme S4. Reagents and conditions: (a) Tosyl chloride, pyridine, DCM, 0ºC to rt, 16 h, 86%; (b) 4-hydroxyphenylboronic acid pinacol ester, Cs_2CO_3, DMF, 90ºC, 16 h, 84%; (c) PS-*p*TsOH, CH_3OH, rt, 18 h, 88%.



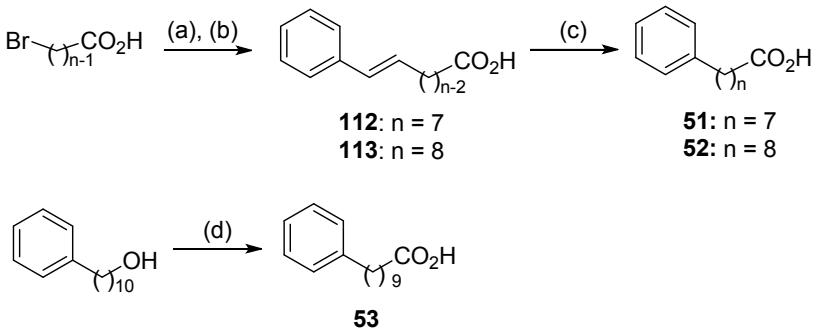
Scheme S5. Reagents and conditions: (a) Triflic anhydride, pyridine, DCM, -20ºC, 30 min; (b) KCN, CH_3CN:H_2O, rt, 12 h, 99%; (c) TFA, CH_3OH, rt, 1.5 h, 61%.



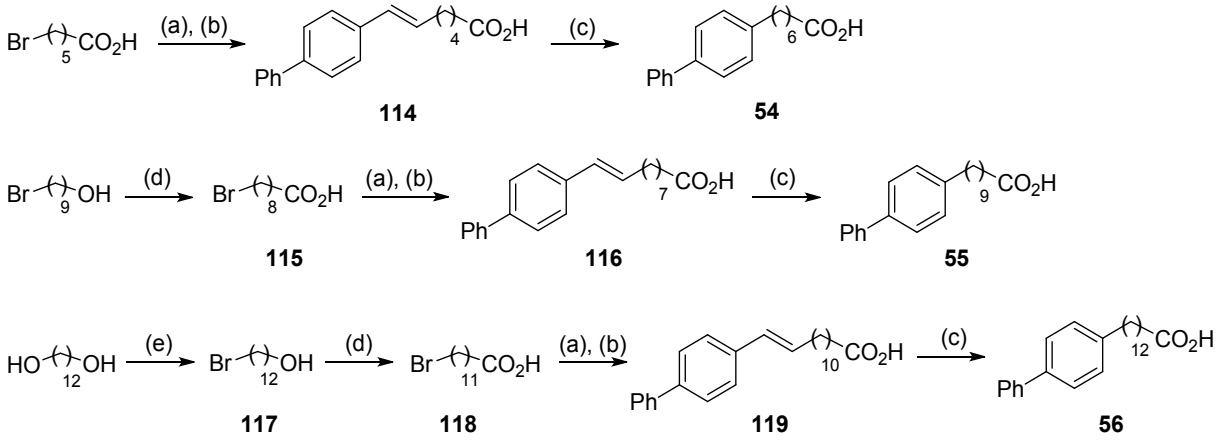
Scheme S6. Reagents and conditions: (a) *p*TsOH, CH_3OH, reflux, 18 h, 99%; (b) [(π-allyl)PdCl]$_2$, 1,3-bis(1-adamantyl)imidazolium chloride, CuI, Cs_2CO_3, DMF:Et_2O, 55ºC, 16 h, 36-44%; (c) $Ni(OAc)_2 \cdot 4H_2O$, $NaBH_4$, ethylenediamine, H_2 (1 atm), EtOH, rt, 2 h, 89-92%; (d) $LiOH \cdot H_2O$, THF:H_2O, rt, 16-18 h, 99%.



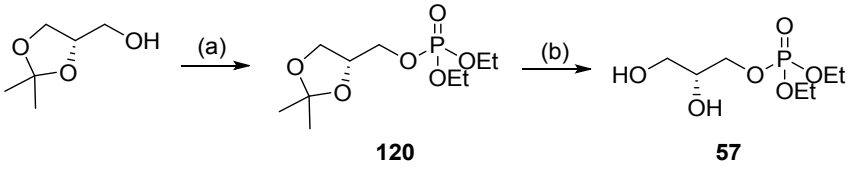
Scheme S7. Reagents and conditions: (a) i) *i*$Pr_2NP(OtBu)_2$, 1*H*-tetrazole, DCM, rt, 2 h; ii) *m*CPBA, DCM, -30ºC, 90 min, 38%; (b) H_2, 10% Pd/C, EtOH, 60ºC, 99%.



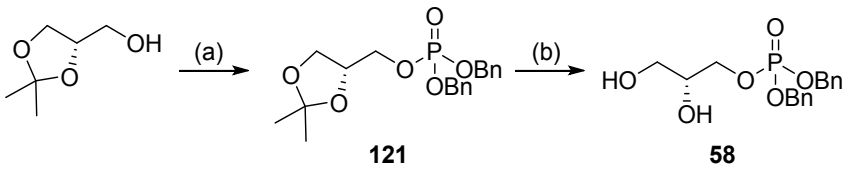
Scheme S8. Reagents and conditions: (a) PPh_3, toluene, reflux, 18 h, 99%; (b) benzaldehyde, lithium bis(trimethylsilyl)amide, THF, -20ºC to rt, 18 h, 61-70%; (c) H_2, 10% Pd/C, EtOH, rt, 81-97%; (d) PDC, DMF, rt, 16 h, 52%.



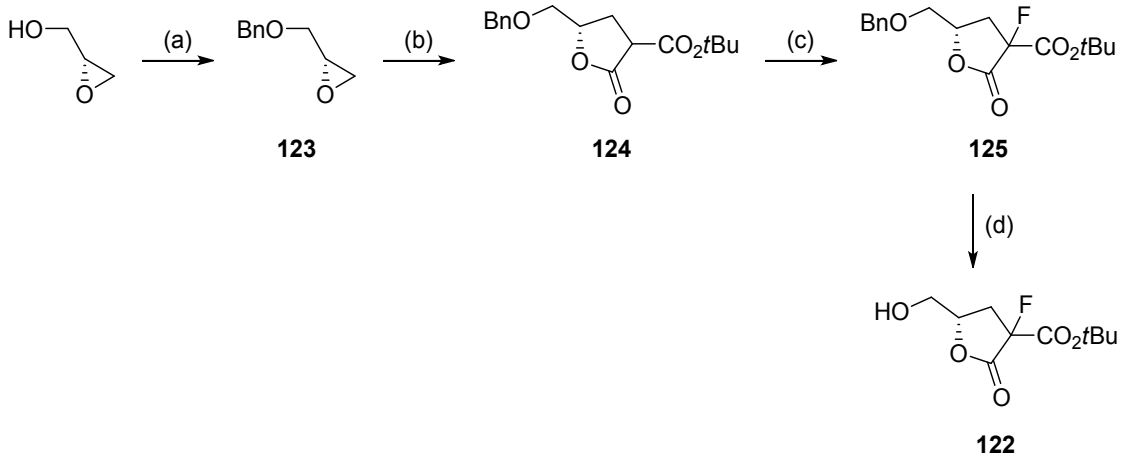
Scheme S9. Reagents and conditions: (a) PPh_3, toluene, reflux, 24 h, 99%; (b) biphenyl-4-carbaldehyde, lithium bis(trimethylsilyl)amide, THF, -20ºC to rt, 18 h, 38-72%; (c) H_2, 10% Pd/C, EtOH, rt, 83-96%; (d) HNO_3, rt to 80ºC, 5 h, 43-61%; (e) 47% aq. HBr, cyclohexane, reflux, 6 h, 65%.



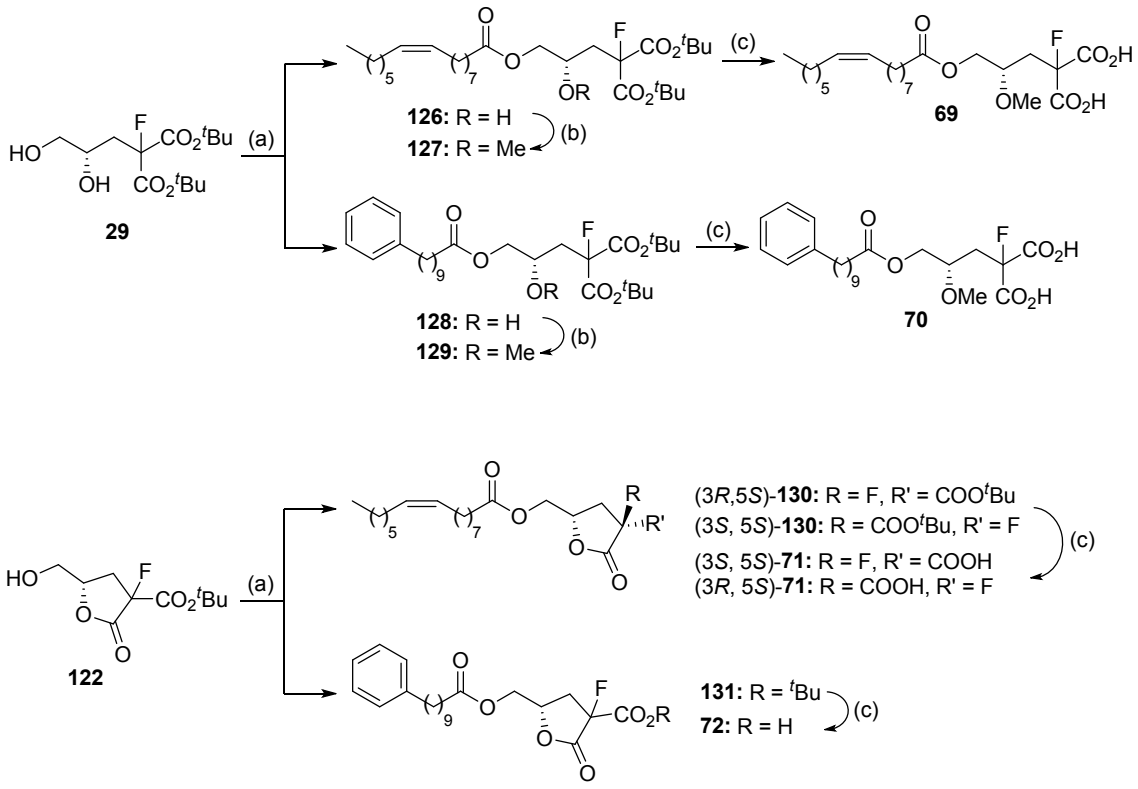
Scheme S10. Reagents and conditions: (a) $ClP(O)(OEt)_2$, KO*t*Bu, DCM, rt, 48 h, 92%; (b) PS-*p*TsOH, CH_3OH, rt, 16 h, 50%.



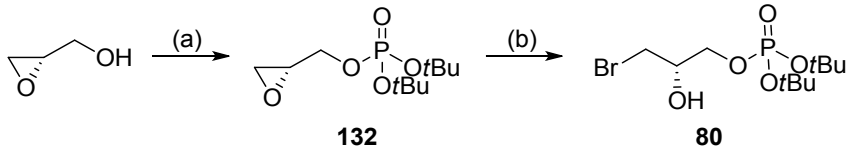
Scheme S11. Reagents and conditions: (a) i) *i*$Pr_2NP(OBn)_2$, 1*H*-tetrazole, DCM, rt, 2 h; ii) *m*CPBA, DCM, -30ºC, 90 min, 76%; (b) PS-*p*TsOH, CH_3OH, rt, 16 h, 65%.



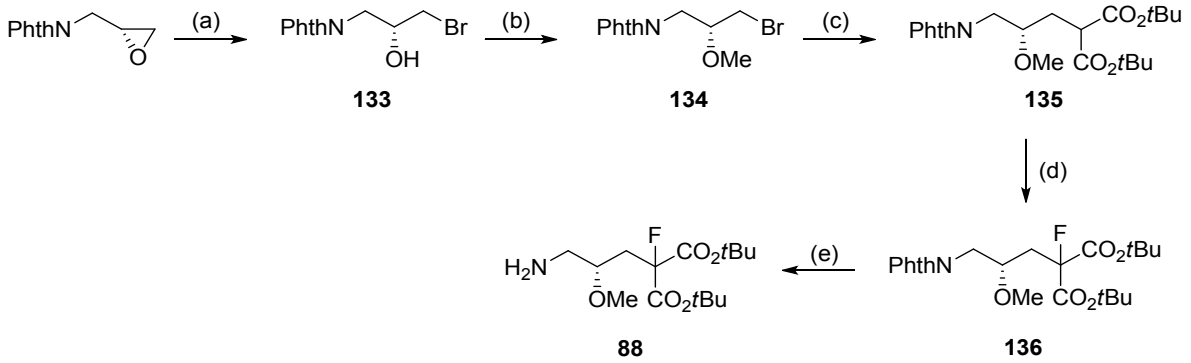
Scheme S12. Reagents and conditions: (a) BnBr, NaH, DMF, 0°C to rt, 18 h, 99%; (b) di-*tert*-butyl malonate, NaH, NaI, DMF:THF, 0ºC to 80ºC, 6 h, 62%; (c) Selectfluor®, NaH, DMF:THF, 0ºC to rt, 48 h, 99%; (d) H_2, 10% Pd/C, EtOH, 60ºC, 99%.



Scheme S13. Reagents and conditions: (a) palmitoleic acid or **53**, DCC, DMAP, -20ºC to rt, 18 h, 21-75%; (b) $TMSCHN_2$, HBF_4, DCM, 0°C, 90 min, 27-30%; (c) TFA, DCM, rt, 18 h, 68-93%.

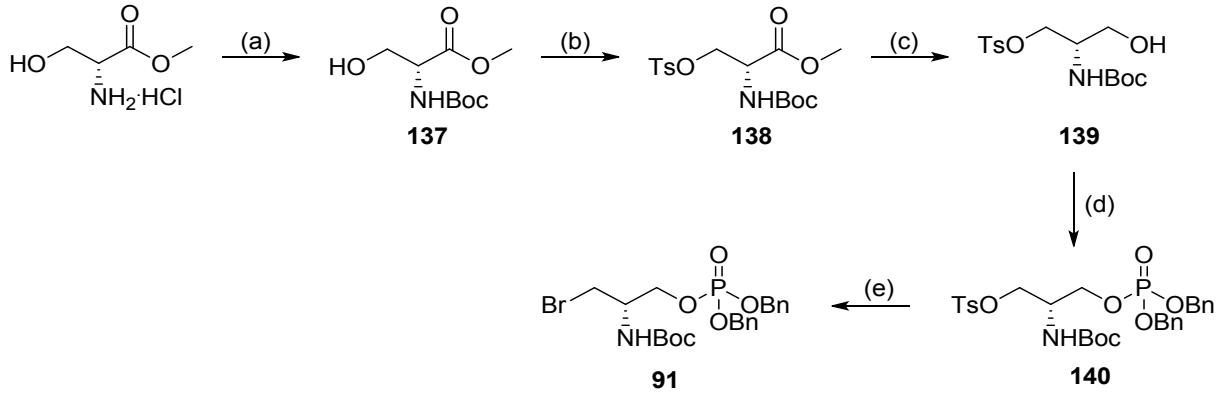


Scheme S14. Reagents and conditions: (a) i) $iPr_2NP(tBu)_2$, 1*H*-tetrazole, DCM, rt, 2 h; ii) *m*CPBA, DCM, -30ºC, 90 min, 52%; (b) TBABr, TFA, $CHCl_3$, rt, 10 min, 95%.



133 134 135 136 88

Scheme S15. Reagents and conditions: (a) HBr, $CHCl_3$, 0°C, 30 min, 96%; (b) $TMSCHN_2$, HBF_4, DCM, 0°C, 2 h, 62%; (c) di-*tert*-butyl malonate, NaH, NaI, DMF, rt, 12 h, 54%; (d) Selectfluor®, NaH, DMF:THF, 0ºC to rt, 48 h, 96%; (e) N_2H_4, EtOH, reflux, 3 h, 66%.



137 138 139 91 140

Scheme S16. Reagents and conditions: (a) Boc_2O, Et_3N, THF, MW, 140°C, 20 min, 99%; (b) *p*TSCl, pyridine, DCM, 0°C to rt, 24 h, 49%; (c) $NaBH_4$, EtOH, -5°C, 1 h, 96%; (d) i) $iPr_2NP(OBn)_2$, 1*H*-tetrazole, DCM, rt, 2 h; ii) *m*CPBA, DCM, -30ºC, 90 min, 38%; (e) LiBr, acetone, reflux, 12 h, 79%.

4. Synthesis and Characterization Data

4.1. General Procedures

General procedure 3: hydrogenation of alkenes and deprotection of benzyl ethers. The corresponding alkene or benzyl ether was dissolved in absolute ethanol (0.2 mL/mg) and the solution was pumped through a H-Cube® continuous-flow hydrogenation reactor using a 10% Pd/C CatCart® cartridge, under full-H_2 mode at a flow-rate of 1 mL/min at rt (for alkenes) or 60°C (for benzyl ethers). Solvent was then removed under reduced pressure to afford the corresponding compound in quantitative yield, which was used without further purification.

General procedure 4: mesylation of alcohols. To a cooled (0°C) stirred solution of the corresponding alcohol (1 equiv) and triethylamine (3 equiv) in anhydrous DCM (3.5 mL/mmol), methanesulfonyl chloride (1.5 equiv) was added dropwise. The reaction mixture was stirred at 0°C for 10 min and then at rt for 1 h. Afterward, the mixture was partitioned between EtOAc and brine. The organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$ and with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the corresponding mesylate, which was used in the next step without further purification.

General procedure 5: tosylation of alcohols. To a cooled (0°C) stirred solution of the corresponding alcohol (1 equiv) and pyridine (3 equiv) in anhydrous DCM (1.2 mL/mmol), *p*-toluenesulfonyl chloride (1.5 equiv) was added portionwise. The reaction mixture was stirred at 0°C for 10 min and then at rt for 16 h. Afterward, the mixture was washed with water and with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the corresponding tosylated derivative.

General procedure 6: di-*tert*-butyl malonate alkylation. Di-*tert*-butyl malonate (1.5 equiv) was added dropwise to a stirred suspension of NaH (1.5 equiv, 60% dispersion in oil) in a 2:1 mixture of anhydrous *N,N*-dimethylformamide (DMF)/THF (6 mL/mmol) at 0ºC, and the mixture was stirred at rt for 15 min. A solution of the corresponding mesylate (1 equiv) in anhydrous THF (3 mL/mmol) was added, followed by sodium iodide (1.1 equiv), and the resulting mixture was heated at 80ºC overnight. Afterward, the reaction was cooled to rt and quenched by addition of a saturated aqueous solution of NH_4Cl. The mixture was then diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to afford the corresponding alkylated product.

General procedure 7: α-fluorination of malonate derivatives. The corresponding malonate derivative (1 equiv) was added to a suspension of NaH (2 equiv, 60% dispersion in oil) in anhydrous THF (4 mL/mmol) at 0ºC, and the reaction mixture was warmed up to rt and then stirred at 70°C for 12 h. The solution was cooled to rt and diluted with anhydrous THF (8 mL/mmol) and DMF (8 mL/mmol). Afterward, Selectfluor® was added (2 equiv) at 0ºC and the solution was stirred at this temperature for 4 h and at rt overnight. The reaction mixture was quenched by addition of water and extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the corresponding fluorinated derivative.

General procedure 8: deprotection of acetals using polystyrene-supported *p*TsOH. The corresponding acetal (1 equiv) was dissolved in methanol (3 mL/g resin) and polystyrene-supported *p*TsOH (PS-*p*TsOH) was added (0.3 equiv, 4.56 mmol *p*TsOH/g resin). The reaction was stirred at rt overnight. Afterward, the mixture was

filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography to afford the corresponding diol.

General procedure 9: regioselective esterification of oleoyl chloride with diols. To a stirred solution of the corresponding diol (1.5 equiv) in anhydrous DCM (12 mL/mmol) at -78°C, 2,4,6-collidine (2 equiv) and oleoyl chloride (1 equiv) were added. The mixture was stirred for 24 h while gradually warming to rt. After this time, solvent was evaporated under reduced pressure and the residue was treated with EtOAc, removing the 2,4,6-collidine hydrochloride by filtration. The filtrate was concentrated and the crude was purified by flash chromatography to yield the corresponding ester.

General procedure 10: methylation of alcohols with trimethylsilyldiazomethane. To a vigorously stirred mixture of the corresponding alcohol (1 equiv) and tetrafluoroboric acid (1 equiv, 35% aqueous solution) in anhydrous DCM (4 mL/mmol) at 0ºC, trimethylsilyldiazomethane (1 equiv, 2 M in diethyl ether) was added dropwise, waiting for the yellow colour to disappear before each addition. The stirring was continued at 0ºC and three further portions of trimethylsilyldiazomethane (0.5 equiv, 0.25 equiv and 0.25 equiv) were added dropwise at intervals of 20 min. Afterward, the mixture was stirred at 0ºC for further 30 min, poured into water and extracted with DCM. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the pure compound.

General procedure 11: Sonogashira coupling reaction of alkynes with methyl-8-bromooctanoate. 1,3-Bis(1-adamantyl)imidazolium chloride (0.15 equiv), CuI (0.225 equiv), $[(\pi\text{-allyl})PdCl]_2$ (0.075 equiv), and Cs_2CO_3 (1.4 equiv) were added in turn to a thoroughly dried vial. A 2:1 mixture of anhydrous diethyl ether and DMF (1.5

mL/mmol ester) was added, followed by the corresponding alkyne (1.3 equiv) and methyl-8-bromooctanoate (1 equiv). The vial was sealed with a Teflon-lined cap and the heterogeneous reaction mixture was stirred vigorously at 55ºC for 16 h. The solvents were then evaporated under reduced pressure and the residue was purified by flash chromatography to yield the desired coupled product.

General procedure 12: stereoselective *cis*-hydrogenation of alkynes with P-2 Ni catalyst. $Ni(OAc)_2 \cdot 4H_2O$ (0.2 equiv) was suspended in absolute ethanol (3 mL/mmol alkyne) at rt. $NaBH_4$ (0.2 equiv) was added and the mixture was stirred for 15 min. Then, argon atmosphere was replaced by hydrogen (balloon). Freshly distilled ethylenediamine was added (1.5 equiv) and the reaction was stirred for 15 min. A solution of the corresponding alkyne (1 equiv) in absolute ethanol (3 mL/mmol) was then added, and the reaction was stirred under hydrogen atmosphere at rt for 2 h. After this time, the reaction mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford the corresponding *Z*-alkene, which was used in the next step without further purification.

General procedure 13: hydrolysis of methyl esters. The corresponding methyl ester (1 equiv) was dissolved in THF (10 mL/mmol) and a solution of lithium hydroxide (2 equiv) in water (1.5 mL/mmol) was added. The reaction was stirred at rt overnight. Then, the mixture was acidified with a 20% aqueous solution of HCl and extracted with DCM. The organic phase was dried over Na_2SO_4, filtered, and concentrated, affording the corresponding carboxylic acid in quantitative yield.

General procedure 14: phosphorylation of alcohols using phosphoramidites. To a solution of the corresponding alcohol (1 equiv) in anhydrous DCM (12 mL/mmol), 1*H*-tetrazole (3 equiv, 0.45 M in acetonitrile) and the corresponding phosphoramidite (2 equiv) were added at rt and the reaction mixture was stirred until total consumption of the alcohol. Then it was cooled to -30ºC, *m*CPBA (2 equiv) was added and the mixture was stirred at -30ºC for 90 min. The reaction was quenched by addition of a 10% aqueous solution of $Na_2S_2O_3$ (12 mL/mmol alcohol) and allowed to warm to rt. Then, the mixture was extracted with DCM and the extracts were successively washed with a 20% aqueous solution of K_2CO_3 and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the corresponding pure phosphate derivative.

General procedure 15: regioselective esterification of carboxylic acids with diols. To a solution of the corresponding carboxylic acid (1 equiv), DCC (1.1 equiv) and DMAP (0.2 equiv) in anhydrous DCM (10 mL/mmol acid) at -20ºC, a solution of the corresponding diol (2 equiv) in anhydrous DCM (2 mL/mmol) was added and the reaction was stirred overnight while warming up to rt. Afterward, the mixture was concentrated under reduced pressure, and the residue was dissolved in carbon tetrachloride and filtered to remove dicyclohexylurea. The filtrate was evaporated and purified by flash chromatography to afford the corresponding pure ester.

General procedure 16: Wittig reaction of ω-bromoacids and aromatic aldehydes. A mixture of the corresponding ω-bromoacid (1.2 equiv) and triphenylphosphine (6 equiv) in anhydrous toluene (2.4 mL/mmol) was refluxed for 24 h. Then, the mixture was allowed to cool to rt, the solvent was evaporated and the residue was washed with hexane to remove excess of triphenylphosphine, and dried. The obtained phosphonium salt (1.2 equiv) was dissolved in anhydrous THF (4.2 mL/mmol), and lithium

hexamethyldisilazane (2.7 equiv, 1 M in toluene) was added dropwise at -20ºC, turning the solution orange. The mixture was stirred for 30 min followed by addition of the corresponding aldehyde (1 equiv) at -20ºC and the stirring was continued overnight at rt. The reaction mixture was acidified with 1 M HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography to yield the corresponding alkene.

General procedure 17: ring-opening reaction of epoxides with TBABr. To a solution of the corresponding oxirane (1 equiv) and TBABr (3 equiv) in freshly distilled alcohol-free chloroform (10 mL/mmol), TFA (1.5 equiv) was added and the reaction was stirred for 10 min at rt. Then, the reaction mixture was passed through a silica gel column (5 g/mmol) prepared in chloroform and it was washed with the same solvent (100 mL/mmol). The solvent was evaporated under reduced pressure to give the corresponding bromoalcohol, which was used in the next step without further purification.

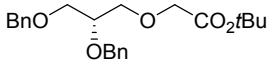
General procedure 18: esterification of carboxylic acids with bromoalcohols and primary alcohols. To a stirred solution of the corresponding carboxylic acid (1 equiv), DCC (1.1 equiv) and DMAP (0.2 equiv) in anhydrous DCM (10 mL/mmol), a solution of the corresponding alcohol (1 equiv) in anhydrous DCM (2 mL/mmol) was added at rt and the reaction was stirred until consumption of the starting material. Afterward, the mixture was concentrated under reduced pressure, and the residue was dissolved in carbon tetrachloride and filtered to remove dicyclohexylurea. The filtrate was concentrated and it was purified by flash chromatography to yield the corresponding ester.

General procedure 19: oxidation of alcohols with nitric acid. To a cooled (0ºC) solution of fuming nitric acid (50 equiv), the corresponding bromoalcohol (1 equiv) was added over a period of 30 minutes, maintaining the reaction temperature at 25-30ºC. The solution was stirred at rt for 4 h and then at 80ºC for an additional hour. The reaction mixture was then cooled back to rt, diluted carefully with water, and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. Flash chromatography afforded the corresponding carboxylic acid.

4.2. Synthesis of intermediates 27-41

4.2.1. Synthesis of diols 27-29

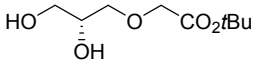
***tert*-Butyl [(2*R*)-2,3-bis(benzyloxy)propoxy]acetate, 94.** (*S*)-(-)-2,3-Bis(benzyloxy)propan-1-ol (0.56 mL, 2.20 mmol, 1 equiv) was added dropwise to a stirred suspension of NaH (176 mg, 4.40 mmol, 2 equiv, 60% dispersion in oil) in anhydrous THF (10 mL) at 0°C. After stirring the mixture at rt for 30 min, *tert*-butyl bromoacetate (0.49 mL, 3.31 mmol, 1.5 equiv) and tetrabutylammonium iodide (TBAI) (41 mg, 0.11 mmol, 0.05 equiv) were added, and the resulting mixture was heated at 50°C overnight. After cooling to rt, the reaction was quenched by addition of water and concentrated under reduced pressure. The residue was dissolved with DCM, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 9:1 to 8:2) to afford pure compound **94** in 22% yield.



94

R_f: 0.52 (hexane/EtOAc, 8:2). IR (ATR): 1738 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 9H, $3CH_3$); 3.47-3.65 (m, 4H, $2CH_2$); 3.72 (qt, J = 4.7, 1H, CH); 3.88 (s, 2H, CH_2CO_2tBu); 4.44 (s, 2H, $PhCH_2$); 4.61 (s, 2H, $PhCH_2$); 7.11-7.29 (m, 10H, $10CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.1 ($3CH_3$); 69.4, 70.4, 71.7 ($3CH_2$); 72.3, 73.4 ($2PhCH_2$); 77.4 (CH); 81.5 (C); 127.5, 127.6 ($2CH_{Ar}$); 127.7 ($2CH_{Ar}$); 127.8 ($2CH_{Ar}$); 128.3 ($2CH_{Ar}$); 128.4 ($2CH_{Ar}$); 138.4, 138.8 ($2C_{Ar}$); 169.6 (CO). MS (ESI, *m/z*): 387.7 $[M+H]^+$.

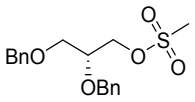
***tert*-Butyl [(2*R*)-2,3-dihydroxypropoxy]acetate, 27.** Following the general procedure 3, diol **27** was obtained from **94** (190 mg, 0.49 mmol) at 60ºC in 95% yield.



27

R_f: 0.11 (hexane/EtOAc, 8:2). IR (ATR): 3376 (O-H); 1738 (C=O). ^{1}H-NMR (methanol-d_4, 300 MHz): δ 1.49 (s, 9H, $3CH_3$); 3.50-3.64 (m, 4H, $2CH_2$); 3.78 (qt, J = 5.3, 1H, CH); 4.87 (s, 2H, CH_2CO_2tBu). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.1 ($3CH_3$); 63.7 (CH_2OH); 68.8 (CH_2CO_2tBu); 70.5 (CH); 73.4 (CH_2O); 82.5 (C); 170.6 (CO). MS (ESI, *m/z*): 229.1 $[M+Na]^+$.

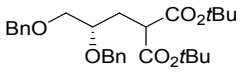
(2*R*)-2,3-Bis(benzyloxy)propyl methanesulfonate, 95. Following the general procedure 4, mesylate **95** was obtained from (*S*)-(-)-2,3-bis(benzyloxy)propan-1-ol (0.35 mL, 1.39 mmol) in 80% yield.



95

R_f: 0.51 (hexane/EtOAc, 7:3). IR (ATR): 1354 (SO_2). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.95 (s, 3H, CH_3); 3.60 (dd, *J* = 4.8, 1.5, 2H, CH_2OBn); 3.86 (m, 1H, CH); 4.31 (dd, *J* = 11.0, 5.6, 1H, ½CH_2OMs); 4.43 (dd, *J* = 11.0, 3.7, 1H, ½CH_2OMs); 4.54 (s, 2H, PhCH_2); 4.66 (s, 2H, PhCH_2); 7.27-7.39 (m, 10H, 10CH_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 37.5 (CH_3); 68.5, 69.4 (2CH_2); 72.5, 73.6 (2PhCH_2); 75.7 (CH); 127.8 (2CH_{Ar}); 127.9 (2CH_{Ar}); 127.91 (2CH_{Ar}); 128.0 (2CH_{Ar}); 128.5 (2CH_{Ar}); 137.7 (2C_{Ar}). MS (ESI, *m/z*): 368.2 $[M+NH_4]^+$.

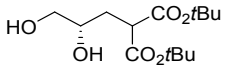
Di-*tert*-butyl [(2*S*)-2,3-bis(benzyloxy)propyl]propanedioate, 96. Following the general procedure 6, compound **96** was obtained from mesylate **95** (391 mg, 1.12 mmol) in 76% yield. Chromatography: hexane to hexane/EtOAc, 9:1.



96

R_f: 0.65 (hexane/EtOAc, 9:1). IR (ATR): 1727 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.42 (s, 9H, 3CH_3); 1.45 (s, 9H, 3CH_3); 2.04-2.10 (m, 2H, CH_2CH(CO_2tBu)$_2$); 3.46 (dd, *J* = 8.9, 6.0, 1H, CH(CO_2tBu)$_2$); 3.55 (dd, *J* = 4.8, 0.8, 2H, CH_2OBn); 3.62-3.68 (m, 1H, CHOBn); 4.53 (d, *J* = 11.5, 1H, ½PhCH_2); 4.54 (s, 2H, PhCH_2); 4.69 (d, *J* = 11.5, 1H, ½PhCH_2); 7.31-7.38 (m, 10H, 10CH_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 27.9 (3CH_3); 28.0 (3CH_3); 31.3 (CH_2CH(CO_2tBu)$_2$); 50.4 (CH(CO_2tBu)$_2$); 72.4, 72.8 (2PhCH_2); 73.4 (CH_2OBn); 76.0 (CHOBn); 81.4 (2C); 127.55, 127.58 (2CH_{Ar}); 127.6 (2CH_{Ar}); 127.9 (2CH_{Ar}); 128.3 (2CH_{Ar}); 128.4 (2CH_{Ar}); 138.6 (2C_{Ar}); 169.0 (2CO). MS (ESI, *m/z*): 471.2 $[M+H]^+$.

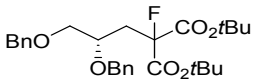
Di-*tert*-butyl [(2*S*)-2,3-dihydroxypropyl]propanedioate, 28. Following the general procedure 3, diol **28** was obtained from **96** (327 mg, 0.74 mmol) at 60ºC in quantitative yield.



28

R_f: 0.37 (hexane/EtOAc, 8:2). IR (ATR): 3408 (O-H); 1726 (C=O). ^{1}H-NMR (methanol-d_4, 300 MHz): δ 1.46 (s, 9H, $3CH_3$); 1.47 (s, 9H, $3CH_3$); 1.76 (ddd, J = 14.8, 9.6, 5.3, 1H, ½CH_2CH(CO_2tBu)$_2$); 2.02 (ddd, J = 14.8, 9.5, 3.3, 1H, ½CH_2CH(CO_2tBu)$_2$); 3.39-3.48 (m, 3H, CH_2OH, CH(CO_2tBu)$_2$); 3.52-3.63 (m, 1H, CHOH). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 28.2 ($3CH_3$); 28.23 ($3CH_3$); 33.7 (CH_2CH(CO_2tBu)$_2$); 52.0 (CH(CO_2tBu)$_2$); 67.4 (CH_2OH); 70.9 (CHOH); 82.7 (2C); 170.4, 170.8 (2CO). MS (ESI, *m/z*): 289.1 $[M-H]^-$

Di-*tert*-butyl [(2*S*)-2,3-bis(benzyloxy)propyl](fluoro)propanedioate, 97. Following the general procedure 7, compound **97** was obtained from **96** (400 mg, 0.85 mmol) in quantitative yield. Chromatography: hexane to hexane/EtOAc, 8:2.

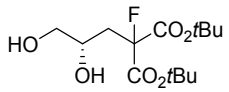


97

R_f: 0.53 (hexane/EtOAc, 8:2). IR (ATR): 1736 (C=O); 1148 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 9H, $3CH_3$); 1.45 (s, 9H, $3CH_3$); 2.24-2.38 (m, 2H, CH_2CF); 3.53 (d, J = 4.8, 2H, CH_2OBn); 3.85-3.93 (m, 1H, CH); 4.51 (d, J = 11.3, 1H, ½PhCH_2); 4.51 (s, 2H, PhCH_2); 4.60 (d, J = 11.3, 1H, ½PhCH_2); 7.28-7.33 (m, 10H, $10CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 27.7 ($3CH_3$); 27.8 ($3CH_3$); 36.6 (CH_2CF); 72.6, 73.0 (2PhCH_2); 73.3 (CH_2OBn); 74.7 (CH); 82.4, 82.8 (2C(CH_3)$_3$); 127.5 ($2CH_{Ar}$); 127.6

(2CH_{Ar}); 128.1 (2CH_{Ar}); 128.32 (2CH_{Ar}); 128.33 (2CH_{Ar}); 138.35, 138.7 (2C_{Ar}); 169.4, 170.1 (2CO); CF not observed. MS (ESI, *m/z*): 506.3 $[M+NH_4]^+$.

Di-*tert*-butyl [(2*S*)-2,3-dihydroxypropyl](fluoro)propanedioate, 29. Following the general procedure 3, diol **29** was obtained from **97** (211 mg, 0.43 mmol) at 60ºC in quantitative yield.

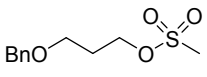


29

R_f: 0.14 (hexane/EtOAc, 8:2). IR (ATR): 3407 (O-H); 1743 (C=O); 1154 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.51 (s, 18H, 6CH_3); 2.18 (dt, *J* = 15.3, 3.0, 1H, ½CH_2CF); 2.34 (ddd, *J* = 15.3, 9.2, 9.0, 1H, ½CH_2CF); 2.91-3.20 (br s, 2H, 2OH); 3.50 (dd, *J* = 11.3, 6.8, 1H, ½CH_2OH); 3.65 (dd, *J* = 11.3, 3.3, 1H, ½CH_2OH); 3.96-4.06 (m, 1H, CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 27.7 (3CH_3); 27.75 (3CH_3); 37.2 (d, *J* = 20.8, CH_2CF); 66.5 (CH_2OH); 67.3 (d, *J* = 2.8, CH); 83.9 (2C$(CH_3)_3$); 93.4 (d, *J* = 196.0, CF); 165.3 (d, *J* = 25.0, CO); 165.8 (d, *J* = 26.1, CO).

4.2.2. Synthesis of alcohols 30, 31

3-(Benzyloxy)propyl methanesulfonate, 98. Following the general procedure 4, mesylate **98** was obtained from benzyloxypropan-1-ol (0.19 mL, 1.20 mmol) in quantitative yield.

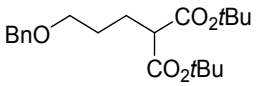


98

R_f: 0.4 (hexane/EtOAc, 5:1). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.04 (qt, *J* = 6.1, 2H, C$H_2$$CH_2$OMs); 2.96 (s, 3H, CH_3); 3.59 (t, *J* = 5.9, 2H, CH_2OBn); 4.36 (t, *J* = 6.2, 2H,

C$\underline{H_2}$OMs); 4.51 (s, 2H, PhC$\underline{H_2}$); 7.27-7.39 (m, 5H, 5CH_{Ar}). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 29.6 ($\underline{C}H_2CH_2OMs$); 37.2 (CH_3); 65.5 ($\underline{C}H_2OMs$); 67.4 ($\underline{C}H_2OBn$); 73.2 (Ph$\underline{C}H_2$); 127.7 (2CH_{Ar}); 127.8 (CH_{Ar}); 128.5 (2CH_{Ar}); 138.1 (C_{Ar}). MS (ESI, *m/z*): 245.1 $[M+H]^+$; 267.0 $[M+Na]^+$.

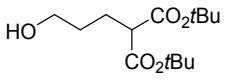
Di-*tert*-butyl [3-(benzyloxy)propyl]propanedioate, 99. Following the general procedure 6, compound **99** was obtained from mesylate **98** (270 mg, 1.11 mmol) in 66% yield. Chromatography: hexane to hexane/EtOAc, 7:3.



99

$\underline{R_f}$: 0.49 (hexane/EtOAc, 8:2). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.45 (s, 18H, 6CH_3); 1.60-1.70 (m, 2H, C$\underline{H_2}CH_2CH$); 1.86-1.94 (m, 2H, C$\underline{H_2}CH$); 3.14 (t, J = 7.5, 1H, CH); 3.49 (t, J = 6.4, 2H, C$\underline{H_2}$OBn); 4.50 (s, 2H, PhC$\underline{H_2}$); 7.24-7.37 (m, 5H, 5CH_{Ar}). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.4 ($\underline{C}H_2CH$); 27.4 ($\underline{C}H_2CH_2CH$); 28.0 (6CH_3); 53.7 (CH); 69.8 ($\underline{C}H_2OBn$); 72.9 (Ph$\underline{C}H_2$); 81.3 (2C); 127.5 (CH_{Ar}); 127.6 (2CH_{Ar}); 128.4 (2CH_{Ar}); 138.5 (C_{Ar}); 168.9 (2CO). MS (ESI, *m/z*): 365.3 $[M+H]^+$; 387.1 $[M+Na]^+$.

Di-*tert*-butyl (3-hydroxypropyl)propanedioate, 30. Following the general procedure 3, alcohol **30** was obtained from **99** (260 mg, 0.68 mmol) at 60ºC in quantitative yield.

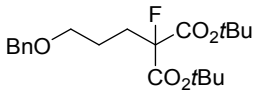


30

$\underline{R_f}$: 0.63 (hexane/EtOAc, 1:1). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.46 (s, 18H, 6CH_3); 1.56-1.67 (m, 2H, C$\underline{H_2}CH_2CH$); 1.86-1.93 (m, 2H, C$\underline{H_2}CH$); 3.16 (t, J = 7.4, 1H,

CH); 3.65 (t, J = 6.3, 2H, C$\underline{H}_2$OH). $\underline{^{13}\text{C-NMR (DMSO-}d_6\text{, 75 MHz)}}$: δ 24.8 ($\underline{C}H_2$CH); 27.9 (6$CH_3$); 30.4 ($\underline{C}H_2CH_2CH$); 53.6 (CH); 62.3 ($CH_2OH$); 81.5 (2C); 169.0 (2CO). $\underline{\text{MS (ESI, } m/z\text{)}}$: 297.1 $[M+Na]^+$.

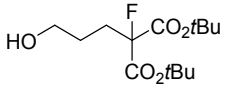
Di-*tert*-butyl [3-(benzyloxy)propyl](fluoro)propanedioate, 100. Following the general procedure 7, compound **100** was obtained from **99** (250 mg, 0.71 mmol) in quantitative yield, which was used in next step without further purification.



100

$\underline{R_f}$: 0.82 (hexane/EtOAc, 8:2). $\underline{^1\text{H-NMR (DMSO-}d_6\text{, 300 MHz)}}$: δ 1.49 (s, 18H, 6$CH_3$); 1.59-1.77 (m, 2H, C$\underline{H}_2CH_2CF$); 2.00-2.24 (m, 2H, CH_2CF); 3.46-3.52 (m, 2H, C$\underline{H}_2$OBn); 4.49 (s, 2H, PhC$\underline{H}_2$); 7.28-7.37 (m, 5H, 5CH_{Ar}). $\underline{^{13}\text{C-NMR (DMSO-}d_6\text{, 75 MHz)}}$: δ 23.6 (d, J = 2.9, $\underline{C}H_2CH_2CF$); 28.2 (6CH_3); 31.2 (d, J = 21.8, C$\underline{H}_2$CF); 70.0 ($\underline{C}H_2$OBn); 73.1 (Ph$\underline{C}H_2$); 83.8 (2$\underline{C}(CH_3)_3$); 100.9 (d, J = 165.6, CF); 127.9 (CH_{Ar}); 128.0 (2CH_{Ar}); 128.8 (2CH_{Ar}); 138.9 (C_{Ar}); 165.7 (d, J = 25.7, 2CO). $\underline{\text{MS (ESI, } m/z\text{)}}$: 400.2 $[M+NH_4]^+$; 405.2 $[M+Na]^+$.

Di-*tert*-butyl fluoro(3-hydroxypropyl)propanedioate, 31. Following the general procedure 3, alcohol **31** was obtained from **100** (329 mg, 0.86 mmol) at 60ºC in quantitative yield.



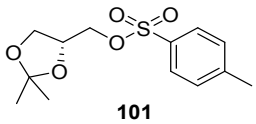
31

$\underline{R_f}$: 0.31 (hexane/EtOAc, 4:1). $\underline{^1\text{H-NMR (DMSO-}d_6\text{, 300 MHz)}}$: δ 1.50 (s, 18H, 6$CH_3$); 1.54-1.71 (m, 2H, C$\underline{H}_2CH_2CF$); 1.91-2.20 (m, 2H, CH_2CF); 3.45-3.64 (m, 2H,

$C\underline{H_2}OH$). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 26.1 (d, J = 2.5, $\underline{C}H_2CH_2CF$); 27.8 ($6CH_3$); 30.2 (d, J = 21.8, $\underline{C}H_2CF$); 62.1 (CH_2OH); 83.5 ($2\underline{C}(CH_3)_3$); 96.0 (d, J = 196.0, CF); 165.6 (d, J = 25.8, 2CO). MS (ESI, *m/z*): 293.1 $[M+H]^+$.

4.2.3. Synthesis of diols 32, 33

[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzene-1-sulfonate, 101. Following the general procedure 5, tosylate **101** was obtained from (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (0.5 mL, 4.05 mmol) in 86% yield. Chromatography: hexane to hexane/EtOAc, 1:1.

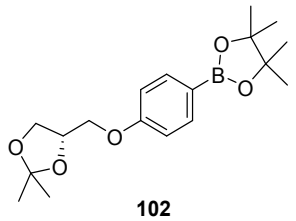


101

R_f: 0.28 (hexane/EtOAc, 5:1). IR (ATR): 1364 (SO_2); 1179 (SO_2). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.31 (s, 3H, CH_3); 1.34 (s, 3H, CH_3); 2.45 (s, 3H, CH_3C_{Ar}); 3.77 (dd, J = 8.8, 5.1, 1H, ½CH_2O); 3.94-4.06 (m, 3H, CH_2OS, ½CH_2O); 4.24-4.31 (m, 1H, CH); 7.35 (d, J = 8.1, 2H, $2CH_{Ar}$); 7.80 (d, J = 8.3, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.8 ($\underline{C}H_3C_{Ar}$); 25.3, 26.8 ($2CH_3$); 66.4 (CH_2O); 69.6 (CH_2OS); 73.1 (CH); 110.2 (C); 128.2 ($2CH_{Ar}$); 130.1 ($2CH_{Ar}$); 132.8, 145.2 ($2C_{Ar}$). $[\alpha]_D^{20}$: -4.2 (c = 1.41, methanol). MS (ESI, *m/z*): 287.1 $[M+H]^+$.

2-(4-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 102. To a solution of tosylate **101** (343 mg, 1.2 mmol, 1.2 equiv) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (220 mg, 1.0 mmol, 1 equiv) in anhydrous DMF (5 mL), Cs_2CO_3 (652 mg, 2.0 mmol, 2 equiv) was added. The

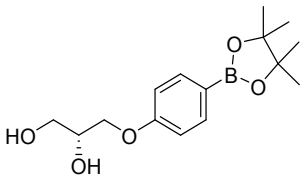
mixture was heated at 90ºC for 16 h. Afterward, the mixture was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane to hexane/EtOAc, 7:3) to afford pure compound **102** in 84% yield.



102

R_f: 0.63 (hexane/EtOAc, 8:2). IR (ATR): 1362 (B-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 12H, $4CH_{3\ boronate}$); 1.40 (s, 3H, $CH_{3\ acetal}$); 1.46 (s, 3H, $CH_{3\ acetal}$); 3.90 (dd, *J* = 8.5, 5.8, 1H, ½CH_2O); 3.96 (dd, *J* = 9.6, 6.0, 1H, ½CH_2O); 4.08 (dd, *J* = 9.5, 5.4, 1H, ½CH_2O); 4.17 (dd, *J* = 8.5, 6.4, 1H, ½CH_2O); 4.48 (qt, *J* = 5.9, 1H, CH); 6.90 (d, *J* = 8.7, 2H, $2CH_{Ar}$); 7.74 (d, *J* = 8.6, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.0 ($4CH_{3\ boronate}$); 25.5, 26.9 ($2CH_{3\ acetal}$); 67.0, 68.7 ($2CH_2$); 74.1 (CH); 83.7 ($2C_{boronate}$); 109.9 (C_{acetal}); 114.0 ($2CH_{Ar}$); 136.7 ($2CH_{Ar}$); 161.2 (C_{Ar}); CB not observed. $[\alpha]_D^{20}$: +9.2 (c = 0.6, $CHCl_3$). MS (ESI, *m/z*): 335.2 $[M+H]^+$.

(2*R*)-3-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]propane-1,2-diol, 32. Following the general procedure 8, diol **32** was obtained from **102** (425 mg, 1.27 mmol) in 88% yield. Chromatography: hexane/EtOAc, 1:1 to 2:8.

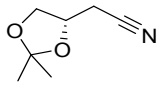


32

R_f: 0.05 (hexane/EtOAc, 7:3). IR (ATR): 3372 (O-H); 1361 (B-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 12H, $4CH_3$); 2.76 (br s, 2H, OH); 3.72 (dd, *J* = 11.5, 5.5, 1H, ½CH_2OAr); 3.82 (dd, *J* = 11.5, 3.7, 1H, ½CH_2OAr); 4.02-4.04 (m, 2H, CH_2OH); 4.06-4.13 (m, 1H, CH); 6.88 (d, *J* = 8.7, 2H, $2CH_{Ar}$); 7.74 (d, *J* = 8.7, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.0 ($4CH_3$); 63.7 (CH_2OH); 69.0 (CH_2OAr); 70.5 (CH); 83.8 (2C); 114.0 ($2CH_{Ar}$); 136.7 ($2CH_{Ar}$); 161.1 (C_{Ar}); CB not observed. $[\alpha]_D^{20}$: +14.2 (c = 1.70, methanol). MS (ESI, *m/z*): 295.1 $[M+H]^+$; 312.2 $[M+NH_4]^+$.

[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]acetonitrile, 103. To a solution of (*S*)-(+)-1,2-isopropylideneglycerol (0.37 mL, 3.0 mmol, 1 equiv) in anhydrous DCM (13.6 mL), pyridine (0.98 mL, 12.1 mmol, 4 equiv) and triflic anhydride (1.0 mL, 6.1 mmol, 2 equiv) were added at -20ºC. The reaction mixture was stirred at this temperature for 30 min. Afterward, the mixture was poured into cold 1M HCl (5 mL) and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the corresponding triflate derivative, which was used in the next step without further purification.

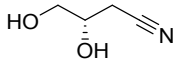
To a solution of triflate derivative (793 mg, 3.0 mmol, 1 equiv) in a 7.5:1 mixture of acetonitrile:water (2.8 mL), KCN (234 mg, 3.6 mmol, 1.2 equiv) was added, and the mixture was stirred at rt overnight. Then it was concentrated under reduced pressure and the residue was dissolved in EtOAc and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford nitrile derivative **103** in quantitative yield, without needing further purification.



103

R_f: 0.44 (hexane/EtOAc, 8:2). IR (ATR): 2251 (CN); 1070 (C-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H, CH_3); 1.45 (s, 3H, CH_3); 2.54-2.68 (dd, *J* = 5.7, 3.1, 2H, CH_2CN); 3.78 (dd, *J* = 8.7, 5.5, 1H, ½CH_2O); 4.14 (dd, *J* = 8.7, 6.0, 1H, ½CH_2O); 4.33 (qt, *J* = 5.7, 1H, CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 22.8 (CH_2CN); 25.4, 26.9 ($2CH_3$); 68.3 (CH_2O); 71.1 (CH); 110.6 (C); 116.7 (CN). $[\alpha]_D^{20}$: +0.55 (c = 0.84, methanol).

(3*S*)-3,4-Dihydroxybutanenitrile, 33. Nitrile **103** (207 mg, 1.47 mmol, 1 equiv) was treated with a 9:1 mixture of TFA:MeOH (6.6 mL) at rt for 90 min. Afterward, the reaction was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane to hexane/EtOAc, 6:4) to afford pure **33** in 61% yield.

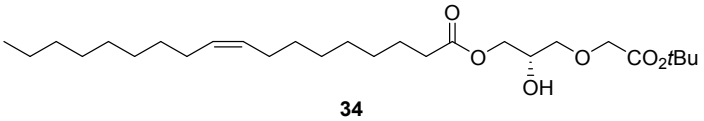


33

R_f: 0.47 (hexane/EtOAc, 1:4). IR (ATR): 3354 (O-H); 2250 (CN); 1026 (C-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.63 (ABX system, *J* = 16.9, 6.8, 4.7, 2H, CH_2CN); 3.53 (ABX system, *J* = 11.2, 5.9, 5.3, 2H, CH_2OH); 3.87 (qt, *J* = 5.7, 1H, CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.8 (CH_2CN); 64.7 (CH_2OH); 68.1 (CH); 118.2 (CN). $[\alpha]_D^{20}$: +0.22 (c = 1.56, methanol).

4.2.4. Synthesis of intermediates 34-41

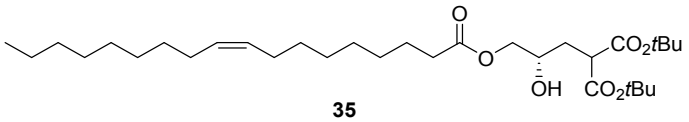
(2*S*)-3-(2-*tert*-Butoxy-2-oxoethoxy)-2-hydroxypropyl (9*Z*)-octadec-9-enoate, 34. Following the general procedure 9, ester **34** was obtained from diol **27** (82 mg, 0.49 mmol) in 36% yield. Chromatography: DCM/EtOAc, 100:1 to 5:1.



34

R_f: 0.52 (DCM/EtOAc, 8:2). IR (ATR): 3460 (O-H); 1739 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.7, 3H, CH_3); 1.23-1.36 (m, 20H, $10CH_2$); 1.48 (s, 9H, $3CH_3$); 1.57-1.69 (m, 2H, CH_2CH_2CO); 1.95-2.06 (m, 4H, $2CH_2CH_{alkene}$); 2.34 (t, *J* = 7.6, 2H, CH_2CO); 3.56 (dd, *J* = 10.0, 6.4, 1H, ½$CHCH_2O$); 3.66 (dd, *J* = 10.0, 3.6, 1H, ½$CHCH_2O$); 3.95-4.07 (m, 3H, CH_2CO_2tBu, CH); 4.11-4.21 (m, 2H, CO_2CH_2); 5.29-5.40 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.2 (CH_3); 22.8, 25.1 ($2CH_2$); 27.3, 27.4 ($2CH_2CH_{alkene}$); 28.3 ($3CH_3$); 29.3 ($2CH_2$); 29.32 (CH_2); 29.5 ($2CH_2$); 29.7, 29.8, 29.9, 32.1 ($4CH_2$); 34.3 (CH_2CO); 65.2 (CO_2CH_2); 69.0 (CH); 69.2 (CH_2CO_2tBu); 73.4 ($CHCH_2O$); 82.4 (C); 129.9, 130.2 ($2CH_{alkene}$); 170.4 (CO_2tBu); 174.0 (CO). MS (ESI, *m/z*): 493.1 $[M+Na]^+$.

Di-*tert*-butyl [(2*S*)-2-hydroxy-3-{[(9*Z*)-octadec-9-enoyl]oxy}propyl]propanedioate, 35. Following the general procedure 9, ester **35** was obtained from diol **28** (190 mg, 0.72 mmol) in 99% yield. Chromatography: DCM/EtOAc, 100:1 to 5:1.

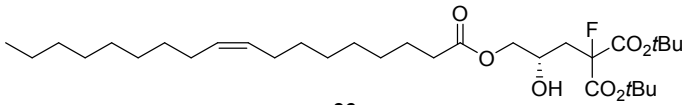


35

R_f: 0.60 (DCM/EtOAc, 9:1). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.7, 3H, CH_3); 1.18-1.37 (m, 20H, $10CH_2$); 1.45 (s, 9H, $3CH_3$); 1.46 (s, 9H, $3CH_3$); 1.56-1.69 (m, 3H, CH_2CH_2CO, ½$CH_2CH(CO_2tBu)_2$); 1.89-2.08 (m, 5H, $2CH_2CH_{alkene}$, ½$CH_2CH(CO_2tBu)_2$); 2.34 (t, *J* = 7.5, 2H, CH_2CO); 3.44 (dd, *J* = 8.1, 6.2, 1H, $CH(CO_2tBu)_2$); 3.84-3.95 (m, 1H, CHOH); 4.01 (dd, *J* = 11.3, 6.7, 1H, ½CO_2CH_2); 4.12 (dd, *J* = 11.3, 3.7, 1H, ½CO_2CH_2); 5.31-5.36 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.2 (CH_3); 22.8, 25.1 ($2CH_2$); 27.3, 27.4 ($2CH_2CH_{alkene}$); 28.0 ($3CH_3$); 28.1 ($3CH_3$); 29.2 ($2CH_2$); 29.3, 29.5, 29.7 ($3CH_2$); 29.8 ($2CH_2$); 29.9, 32.1, 32.4 ($3CH_2$);

34.3 ($\underline{C}H_2CO$); 50.9 ($\underline{C}H(CO_2tBu)_2$); 68.2 (CHOH); 68.3 ($CO_2\underline{C}H_2$); 82.0 (2C); 129.9, 130.2 ($2CH_{alkene}$); 168.9, 169.2 ($2\underline{C}O_2tBu$); 174.0 (CO). MS (ESI, *m/z*): 555.2 $[M+H]^+$.

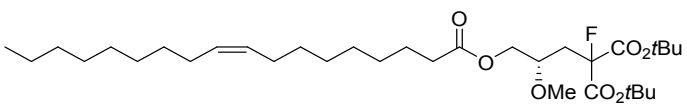
Di-*tert*-butyl fluoro[(2*S*)-2-hydroxy-3-{[(9*Z*)-octadec-9-enoyl]oxy}propyl] propanedioate, 36. Following the general procedure 9, ester **36** was obtained from diol **29** (116 mg, 0.38 mmol) in 60% yield. Chromatography: DCM to DCM/EtOAc, 9:1.



36

$\underline{R_f}$: 0.56 (hexane/EtOAc, 8:2). IR (ATR): 3513 (O-H); 1743 (C=O); 1164 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.6, 3H, CH_3); 1.22-1.37 (m, 20H, $10CH_2$); 1.50 (s, 18H, $6CH_3$); 1.60-1.65 (m, 2H, $C\underline{H}_2CH_2CO$); 1.97-2.03 (m, 4H, $2C\underline{H}_2CH_{alkene}$); 2.23-2.44 (m, 4H, $C\underline{H}_2CO$, $C\underline{H}_2CF$); 3.99-4.21 (m, 3H, CO_2CH_2, CH); 5.32-5.36 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3); 22.7, 24.9 ($2CH_2$); 27.2, 27.24 ($2\underline{C}H_2CH_{alkene}$); 27.7 ($3CH_3$); 27.78 ($3CH_3$); 29.1, 29.2 ($2CH_2$); 29.3 ($2CH_2$); 29.33, 29.5, 29.7, 29.8, 31.9 ($5CH_2$); 34.1 ($\underline{C}H_2CO$); 37.4 (d, *J* = 20.4, CH_2CF); 65.3 (CH); 67.9 ($CO_2\underline{C}H_2$); 83.8, 83.9 ($2\underline{C}(CH_3)_3$); 129.8, 130.0 ($2CH_{alkene}$); 165.5 (d, *J* = 24.8, $\underline{C}O_2tBu$); 166.0 (d, *J* = 25.7, $\underline{C}O_2tBu$); 174.4 (CO); CF not observed. MS (ESI, *m/z*): 590.5 $[M+NH_4]^+$.

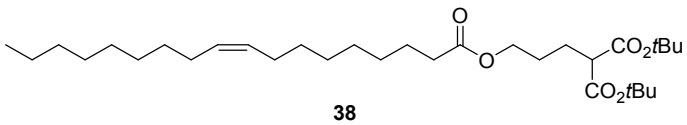
Di-*tert*-butyl fluoro[(2*S*)-2-methoxy-3-{[(9*Z*)-octadec-9-enoyl]oxy}propyl] propanedioate, 37. Following the general procedure 10, compound **37** was obtained from **36** (90 mg, 0.16 mmol) in 38% yield. Chromatography: hexane/EtOAc, 30:1 to 5:1.



37

R_f: 0.41 (hexane/EtOAc, 8:2). IR (ATR): 1769 (C=O); 1165 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, *J* = 6.5, 3H, CH_3); 1.26-1.29 (m, 20H, $10CH_2$); 1.48 (s, 9H, $3CH_3$); 1.49 (s, 9H, $3CH_3$); 1.59-1.64 (m, 2H, CH_2CH_2CO); 1.99-2.01 (m, 4H, $2CH_2CH_{alkene}$); 2.16-2.48 (m, 2H, CH_2CF); 2.32 (t, *J* = 7.5, 2H, CH_2CO); 3.29 (s, 3H, OCH_3); 3.57-3.64 (m, 1H, CH); 4.10 (ABX system, *J* = 11.6, 4.8, 4.6, 2H, CO_2CH_2); 5.28-5.39 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 22.8, 25.0 ($2CH_2$); 27.3, 27.34 ($2CH_2CH_{alkene}$); 27.8 ($3CH_3$); 27.9 ($3CH_3$); 29.2 ($2CH_2$); 29.3 (CH_2); 29.5 ($2CH_2$); 29.7, 29.8, 29.9, 32.0 ($4CH_2$); 34.3 (CH_2CO); 36.7 (d, *J* = 21.4, CH_2CF); 57.9 (OCH_3); 64.9 (CO_2CH_2); 73.9 (d, *J* = 3.3, CH); 83.2, 83.6 ($2C(CH_3)_3$); 92.5 (d, *J* = 195.3, CF); 129.9, 130.1 ($2CH_{alkene}$); 165.1 (d, *J* = 27.4, CO_2tBu); 165.2 (d, *J* = 23.8, CO_2tBu); 173.7 (CO). $[\alpha]_D^{20}$: +4.1 (c = 0.75, $CHCl_3$). MS (ESI, *m/z*): 609.4 $[M+Na]^+$.

Di-*tert*-butyl (3-{[(9*Z*)-octadec-9-enoyl]oxy}propyl)propanedioate, 38. Following the general procedure 9, ester **38** was obtained from alcohol **30** (120 mg, 0.44 mmol) in 70% yield. Cromatography: DCM.

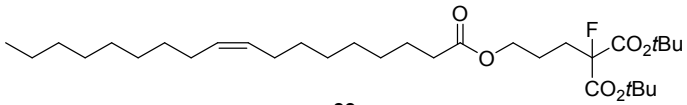


38

R_f: 0.44 (hexane/EtOAc, 1:1). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 0.88 (t, *J* = 6.7, 3H, CH_3); 1.25-1.29 (m, 20H, $10CH_2$); 1.46 (s, 18H, $6CH_3$); 1.54-1.72 (m, 4H, CH_2CH_2CO, $CH_2CH_2CH(CO_2t\text{Bu})_2$); 1.83-1.91 (m, 2H, $CH_2CH(CO_2t\text{Bu})_2$); 1.97-2.03 (m, 4H, $2CH_2CH_{alkene}$); 2.29 (t, *J* = 7.6, 2H, CH_2CO); 3.14 (t, *J* = 7.5, 1H, CH); 4.07 (t, *J* = 6.4, 2H, CO_2CH_2); 5.28-5.39 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 14.2 (CH_3); 22.7; 25.0; 25.2; 26.4 ($4CH_2$); 27.2; 27.24 ($2CH_2CH_{alkene}$); 27.9 ($6CH_3$); 29.1; 29.18; 29.2 ($3CH_2$); 29.4 ($2CH_2$); 29.6; 29.7; 29.8; 31.9 ($4CH_2$); 34.3 (CH_2CO); 53.5

(CH); 63.7 ($CO_2\underline{C}H_2$); 81.5 (2C); 129.9; 130.1 ($2CH_{alkene}$); 168.7 ($2\underline{C}O_2t$Bu); 173.9 (CO).

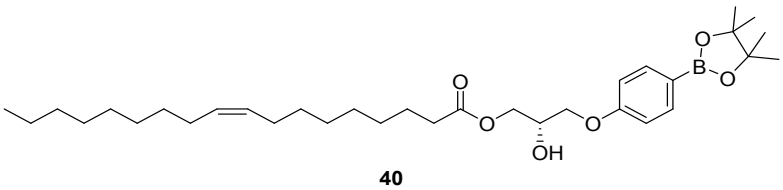
Di-*tert*-butyl fluoro(3-{[(9*Z*)-octadec-9-enoyl]oxy}propyl)propanedioate, 39. Following the general procedure 9, ester **39** was obtained from alcohol **31** (199 mg, 0.68 mmol) in 70% yield. Chromatography: DCM.



39

$\underline{R_f}$: 0.69 (hexane/EtOAc, 1:1). $\underline{^1H\text{-NMR (DMSO-}d_6\text{, 300 MHz)}}$: δ 0.88 (t, *J* = 6.8, 3H, CH_3); 1.23-1.37 (m, 20H, $10CH_2$); 1.46 (s, 3H, CH_3); 1.50 (s, 15H, $5CH_3$); 1.56-1.64 (m, 2H, $C\underline{H_2}CH_2CO$); 1.69-1.79 (m, 2H, $C\underline{H_2}CH_2CF$); 1.97-2.04 (m, 4H, $2C\underline{H_2}CH_{alkene}$); 2.07-2.20 (m, 2H, CH_2CF); 2.29 (t, *J* = 7.6, 2H, CH_2CO); 4.08 (t, *J* = 6.3, 2H, CO_2CH_2); 5.29-5.40 (m, 2H, $2CH_{alkene}$). $\underline{^{13}C\text{-NMR (DMSO-}d_6\text{, 75 MHz)}}$: δ 14.5 ($CH_3$); 22.7 (d, *J* = 3.2, $\underline{C}H_2CH_2CF$); 23.1, 25.3 ($2CH_2$); 27.6, 27.61 ($2\underline{C}H_2CH_{alkene}$); 28.2 ($6CH_3$); 28.3, 29.5, 29.54, 29.6, 29.7, 29.9, 30.1, 30.2 ($8CH_2$); 30.9 (d, *J* = 21.9, $\underline{C}H_2CF$); 32.3 (CH_2); 34.7 ($\underline{C}H_2CO$); 63.9 ($CO_2\underline{C}H_2$); 84.0 ($2\underline{C}(CH_3)_3$); 94.8 (d, *J* = 196.5, CF); 130.2, 130.4 ($2CH_{alkene}$); 165.7 (d, *J* = 25.4, $2\underline{C}O_2t$Bu); 174.2 (CO). $\underline{\text{MS (ESI, }m/z\text{)}}$: 557.5 $[M+H]^+$.

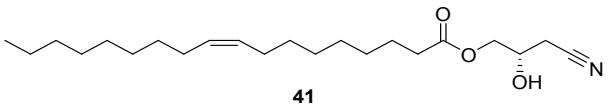
(2*S*)-2-Hydroxy-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy] propyl (9*Z*)-octadec-9-enoate, 40. Following the general procedure 9, ester **40** was obtained from diol **32** (130 mg, 0.44 mmol) in 40% yield. Chromatography: DCM to DCM/ethanol, 100:1.



40

R_f: 0.46 (DCM/ethanol, 20:1). IR (ATR): 3459 (O-H); 1737 (C=O); 1362 (B-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.7, 3H, CH_3); 1.26-1.33 (m, 32H, $10CH_2$, $4CH_{3\ boronate}$); 1.56-1.68 (m, 2H, CH_2CH_2CO); 1.97-2.01 (m, 4H, $2CH_2CH_{alkene}$); 2.35 (t, *J* = 7.5, 2H, CH_2CO); 2.57 (br s, 1H, OH); 4.00-4.09 (m, 2H, CH_2OAr); 4.22-4.32 (m, 3H, CH, CO_2CH_2); 5.28-5.40 (m, 2H, $2CH_{alkene}$); 6.90 (d, *J* = 8.7, 2H, $2CH_{Ar}$); 7.75 (d, *J* = 8.6, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 22.8 (CH_2); 25.0 ($4CH_3$); 25.04 (CH_2); 27.3, 27.4 ($2CH_2CH_{alkene}$); 29.2 ($2CH_2$); 29.3 (CH_2); 29.5 ($2CH_2$); 29.7, 29.8, 29.9, 32.0 ($4CH_2$); 34.3 (CH_2CO); 65.3 (CO_2CH_2); 68.6 (CH_2OAr); 68.8 (CH); 83.8 (2C); 114.0 ($2CH_{Ar}$); 129.9, 130.2 ($2CH_{alkene}$); 136.7 ($2CH_{Ar}$); 161.0 (C_{Ar}); 174.1 (CO); CB not observed. $[\alpha]_D^{20}$: +1.5 (c = 1, $CHCl_3$). MS (ESI, *m/z*): 557.8 $[M-H]^-$.

(2*S*)-3-Cyano-2-hydroxypropyl (9*Z*)-octadec-9-enoate, 41. Following the general procedure 9, ester **41** was obtained from diol **33** (61 mg, 0.60 mmol) in 88% yield. Chromatography: hexane to hexane/EtOAc, 6:4.



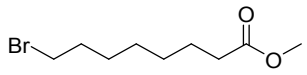
41

R_f: 0.27 (hexane/EtOAc, 8:2). IR (ATR): 3380 (O-H); 2250 (CN); 1740 (C=O); 1115 (C-O); 1093 (C-O). ^{1}H-NMR (methanol-d_4, 300 MHz): δ 0.90 (t, *J* = 6.6, 3H, CH_3); 1.29-1.33 (m, 20H, $10CH_2$); 1.57-1.65 (m, 2H, CH_2CH_2CO); 2.00-2.06 (m, 4H, $2CH_2CH_{alkene}$); 2.36 (t, *J* = 7.6, 2H, CH_2CO); 2.57-2.74 (m, 2H, CH_2CN); 4.04-4.14 (m, 3H, CH, CO_2CH_2); 5.29-5.39 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 13.5 (CH_3); 20.9 (CH_2CN); 22.8, 24.9 ($2CH_2$); 27.2 ($2CH_2CH_{alkene}$); 29.22, 29.24, 29.3, 29.4, 29.5, 29.7, 29.8, 29.9, 32.1 ($9CH_2$); 33.8 (CH_2CO); 65.3 (CH); 66.5 (CO_2CH_2); 118.7 (CN); 129.8, 129.9 ($2CH_{Alkene}$); 173.9 (CO). $[\alpha]_D^{20}$: +0.53 (c = 1.00, methanol). MS (ESI, *m/z*): 383.4 $[M+NH_4]^+$; 388.3 $[M+Na]^+$.

4.3. Synthesis of intermediates 42-50

4.3.1. Synthesis of fatty acids 42-44

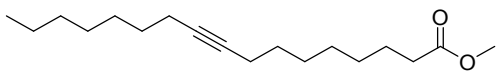
Methyl 8-bromooctanoate, 104. To a solution of 8-bromooctanoic acid (2.0 g, 8.96 mmol, 1 equiv) in methanol (10 mL), concentrated H_2SO_4 (0.2 mL) was added and the reaction mixture was refluxed overnight. Afterward, the solvent was evaporated and the residue was dissolved in EtOAc and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield ester **104** in quantitative yield, which was used in the next step without further purification. The spectroscopic data correspond with those previously reported.[1]



104

R_f: 0.23 (hexane/EtOAc, 20:1). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.30 (m, 4H, $2CH_2$); 1.40-1.45 (m, 2H, CH_2); 1.57-1.67 (m, 2H, CH_2); 1.84 (qt, J = 7.5, 2H, CH_2CH_2CO); 2.30 (t, J = 7.5, 2H, CH_2CO); 3.39 (t, J = 6.8, 2H, CH_2Br); 3.66 (s, 3H, CH_3).

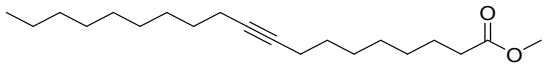
Methyl heptadec-9-ynoate, 105. Following the general procedure 11, alkyne **105** was obtained from 1-nonyne (0.27 mL, 1.64 mmol) and **104** (300 mg, 1.26 mmol) in 36% yield. Chromatography: hexane.



105

R_f: 0.32 (hexane/EtOAc, 20:1). IR (ATR): 1740 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, J = 6.5, 3H, CH_3); 1.28-1.38 (m, 14H, $7CH_2$); 1.42-1.49 (m, 4H, $2CH_2$); 1.58-1.65 (m, 2H, CH_2CH_2CO); 2.13 (t, J = 6.9, 4H, $2CH_2C_{alkyne}$); 2.30 (t, J = 7.5, 2H; CH_2CO); 3.66 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.2 (CH_3); 18.87, 18.9 ($2CH_2C_{alkyne}$); 22.8, 25.1, 28.8, 29.9 ($4CH_2$); 29.0 ($2CH_2$); 29.2, 29.22, 29.3, 31.9 ($4CH_2$); 34.2 (CH_2CO); 51.6 (OCH_3); 80.2, 80.5 ($2C_{alkyne}$); 174.4 (CO).

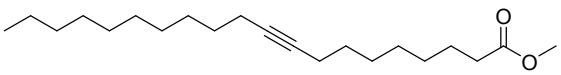
Methyl nonadec-9-ynoate, 106. Following the general procedure 11, alkyne **106** was obtained from 1-undecyne (0.33 mL, 1.64 mmol) and **104** (300 mg, 1.26 mmol) in 38% yield. Chromatography: hexane.



106

R_f: 0.36 (hexane/EtOAc, 20:1). IR (ATR): 1742 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, J = 6.7, 3H, CH_3); 1.27-1.51 (m, 22H, $11CH_2$); 1.57-1.67 (m, 2H, CH_2CH_2CO); 2.11-2.16 (m, 4H, $2CH_2C_{alkyne}$); 2.30 (t, J = 7.5, 2H, CH_2CO), 3.66 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 18.88, 18.9 ($2CH_2C_{alkyne}$); 22.8, 25.1, 28.8, 28.9, 29.0, 29.2, 29.22 ($7CH_2$); 29.3 ($2CH_2$); 29.5, 29.7, 32.1 ($3CH_2$); 34.2 (CH_2CO); 51.6 (OCH_3); 80.2, 80.5 ($2C_{alkyne}$), 174.4 (CO). MS (ESI, *m/z*): 309.3 $[M+H]^+$

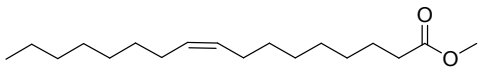
Methyl icos-9-ynoate, 107. Following the general procedure 11, alkyne **107** was obtained from 1-dodecyne (0.32 mL, 1.64 mmol) and **104** (300 mg, 1.26 mmol) in 44% yield. Chromatography: hexane.



107

R_f: 0.48 (hexane/EtOAc, 20:1). IR (ATR): 1740 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.7, 3H, CH_3); 1.26-1.40 (m, 20H, $10CH_2$); 1.42-1.49 (m, 4H, $2CH_2$); 1.57-1.67 (m, 2H, CH_2CH_2CO); 2.13 (t, *J* = 6.9, 4H, $2CH_2C_{alkyne}$); 2.30 (t, *J* = 7.5, 2H, CH_2CO); 3.66 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 18.88, 18.9 ($2CH_2C_{alkyne}$); 22.8, 25.1, 28.8, 28.9, 29.0, 29.2, 29.22 ($7CH_2$); 29.3 ($2CH_2$); 29.5, 29.7, 29.74, 32.1 ($4CH_2$); 34.2 (CH_2CO); 51.6 (OCH_3); 80.2, 80.5 ($2C_{alkyne}$); 174.4 (CO).

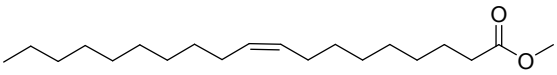
Methyl (9*Z*)-heptadec-9-enoate, 108. Following the general procedure 12, alkene **108** was obtained from alkyne **105** (126 mg, 0.45 mmol) in 91% yield.



108

R_f: 0.32 (hexane/EtOAc, 20:1). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, *J* = 6.6, 3H, CH_3); 1.27-1.29 (m, 18H, $9CH_2$); 1.59-1.63 (m, 2H, CH_2CH_2CO); 1.97-2.06 (m, 4H, $2CH_2CH_{alkene}$); 2.30 (t, *J* = 7.5, 2H, CH_2CO); 3.66 (s, 3H, OCH_3); 5.28-5.39 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 22.8, 25.1 ($2CH_2$); 27.3, 27.4 ($2CH_2CH_{alkene}$); 29.2, 29.26, 29.29, 29.3, 29.4, 29.8, 29.9, 32.0 ($8CH_2$); 34.2 (CH_2CO); 51.6 (OCH_3); 129.9, 130.1 ($2CH_{alkene}$); 174.5 (CO).

Methyl (9*Z*)-nonadec-9-enoate, 109. Following the general procedure 12, alkene **109** was obtained from alkyne **106** (120 mg, 0.39 mmol) in 92% yield.

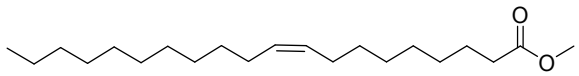


109

R_f: 0.36 (hexane/EtOAc, 20:1). IR (ATR): 1742 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.7, 3H, CH_3); 1.26-1.30 (m, 22H, $11CH_2$); 1.58-1.64 (m, 2H,

C$\underline{H_2}$CH$_2$CO); 1.97-2.01 (m, 4H, 2C$\underline{H_2}$CH$_{alkene}$); 2.30 (t, *J* = 7.5, 2H, CH$_2$CO); 3.66 (s, 3H, OCH$_3$); 5.29-5.40 (m, 2H, 2CH$_{alkene}$). $\underline{^{13}C\text{-NMR (CDCl}_3\text{, 75 MHz)}}$: δ 14.3 (CH$_3$); 22.8, 25.1 (2CH$_2$); 27.3, 27.4 (2$\underline{C}H_2CH_{alkene}$); 29.2, 29.3, 29.31, 29.4, 29.49, 29.7, 29.8, 29.84, 29.9, 32.1 (10CH$_2$); 34.3 ($\underline{C}$H$_2$CO); 51.6 (OCH$_3$); 129.9, 130.2 (2CH$_{alkene}$); 174.5 (CO). $\underline{\text{MS (ESI, } m/z\text{)}}$: 311.3 $[M+H]^+$.

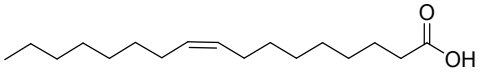
Methyl (9*Z*)-icos-9-enoate, 110. Following the general procedure 12, alkene **110** was obtained from alkyne **107** (128 mg, 0.40 mmol) in 89% yield.



110

$\underline{R_f}$: 0.48 (hexane/EtOAc, 20:1). $\underline{\text{IR (ATR)}}$: 1743 (C=O). $\underline{^1H\text{-NMR (CDCl}_3\text{, 300 MHz)}}$: δ 0.88 (t, *J* = 6.7, 3H, CH$_3$); 1.26-1.30 (m, 24H, 12CH$_2$); 1.57-1.64 (m, 2H, C$\underline{H_2}$CH$_2$CO); 1.97-2.04 (m, 4H, 2C$\underline{H_2}$CH$_{alkene}$); 2.30 (t, *J* = 7.5, 2H, CH$_2$CO); 3.66 (s, 3H, OCH$_3$); 5.29-5.40 (m, 2H, 2CH$_{alkene}$). $\underline{^{13}C\text{-NMR (CDCl}_3\text{, 75 MHz)}}$: δ 14.3 (CH$_3$); 22.8, 25.1 (2CH$_2$); 27.3, 27.4 (2$\underline{C}H_2CH_{alkene}$); 29.2, 29.28, 29.3, 29.4, 29.5, 29.7, 29.8, 29.81, 29.84, 29.9, 32.1 (11CH$_2$); 34.3 ($\underline{C}$H$_2$CO); 51.6 (OCH$_3$); 129.9, 130.2 (2CH$_{alkene}$); 174.5 (CO).

(9*Z*)-Heptadec-9-enoic acid, 42. Following the general procedure 13, carboxylic acid **42** was obtained from ester **108** (115 mg, 0.41 mmol) in quantitative yield.

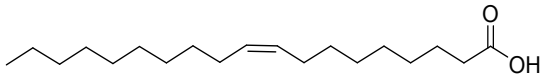


42

$\underline{R_f}$: 0.43 (hexane/EtOAc, 1:1). $\underline{\text{IR (ATR)}}$: 3252 (O-H); 1710 (C=O). $\underline{^1H\text{-NMR (CDCl}_3\text{, 300 MHz)}}$: δ 0.88 (t, *J* = 6.7, 3H, CH$_3$); 1.27-1.31 (m, 18H, 9CH$_2$); 1.58-1.66 (m, 2H,

C$\underline{H_2}$CH$_2$CO); 1.98-2.04 (m, 4H, 2C$\underline{H_2}$CH$_{alkene}$); 2.35 (t, *J* = 7.5, 2H, CH$_2$CO); 5.29-5.40 (m, 2H, 2CH$_{alkene}$). $\underline{^{13}C\text{-NMR (CDCl}_3\text{, 75 MHz)}}$: δ 14.3 (CH$_3$); 22.8, 24.8 (2CH$_2$); 27.3, 27.4 (2$\underline{C}H_2CH_{alkene}$); 29.2, 29.21, 29.3, 29.37, 29.4, 29.8, 29.9, 32.0 (8CH$_2$); 34.2 ($\underline{C}$H$_2$CO); 129.9, 130.2 (2CH$_{alkene}$); 180.0 (CO). $\underline{\text{MS (ESI, } m/z\text{)}}$: 267.1 [M-H]$^-$.

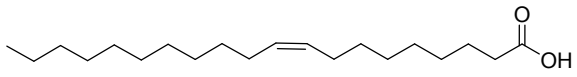
(9*Z*)-Nonadec-9-enoic acid, 43. Following the general procedure 13, carboxylic acid **43** was obtained from ester **109** (111 mg, 0.36 mmol) in quantitative yield.



43

$\underline{R_f}$: 0.45 (hexane/EtOAc, 1:1). $\underline{\text{IR (ATR)}}$: 1710 (C=O). $\underline{^1H\text{-NMR (CDCl}_3\text{, 300 MHz)}}$: δ 0.88 (t, *J* = 6.7, 3H, CH$_3$); 1.26-1.31 (m, 22H, 11CH$_2$); 1.58-1.68 (m, 2H, C$\underline{H_2}$CH$_2$CO); 1.98-2.04 (m, 4H, 2C$\underline{H_2}$CH$_{alkene}$); 2.35 (t, *J* = 7.5, 2H, CH$_2$CO); 5.29-5.40 (m, 2H, 2CH$_{alkene}$). $\underline{^{13}C\text{-NMR (CDCl}_3\text{, 75 MHz)}}$: δ 14.3 (CH$_3$); 22.8, 24.8 (2CH$_2$); 27.3, 27.4 (2$\underline{C}H_2CH_{alkene}$); 29.2, 29.22, 29.3, 29.5, 29.51, 29.7, 29.8, 29.83, 29.9, 32.1 (10CH$_2$); 34.2 ($\underline{C}$H$_2$CO); 129.9, 130.2 (2CH$_{alkene}$); 180.2 (CO).

(9*Z*)-Icos-9-enoic acid, 44. Following the general procedure 13, carboxylic acid **44** was obtained from ester **110** (114 mg, 0.35 mmol) in quantitative yield.



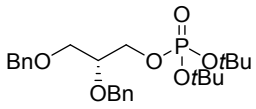
44

$\underline{R_f}$: 0.46 (hexane/EtOAc, 1:1). $\underline{\text{IR (ATR)}}$: 1711 (C=O). $\underline{^1H\text{-NMR (CDCl}_3\text{, 300 MHz)}}$: δ 0.88 (t, *J* = 6.7, 3H, CH$_3$); 1.26-1.31 (m, 24H, 12CH$_2$); 1.56-1.68 (m, 2H, C$\underline{H_2}$CH$_2$CO); 1.94-2.04 (m, 4H, 2C$\underline{H_2}$CH$_{alkene}$); 2.35 (t, *J* = 7.5, 2H, CH$_2$CO); 5.29-5.40 (m, 2H, 2CH$_{alkene}$). $\underline{^{13}C\text{-NMR (CDCl}_3\text{, 75 MHz)}}$: δ 14.3 (CH$_3$); 22.9, 24.8 (2CH$_2$); 27.3, 27.4

($2\underline{C}H_2CH_{alkene}$); 29.2, 29.22, 29.3, 29.5, 29.51, 29.7, 29.8 ($7CH_2$); 29.82 ($2CH_2$); 29.9, 32.1 ($2CH_2$); 34.1 ($\underline{C}H_2CO$); 129.9, 130.2 ($2CH_{alkene}$); 180.0 (CO). MS (ESI, *m/z*): 309.2 $[M-H]^-$.

4.3.2. Synthesis of phosphorylated diol 45

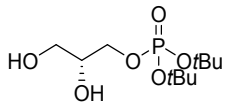
(2*R*)-2,3-Bis(benzyloxy)propyl di-*tert*-butyl phosphate, 111. Following the general procedure 14, compound **111** was obtained from (*S*)-2,3-bis(benzyloxy)propan-1-ol (416 mg, 1.53 mmol) and di-*tert*-butyl-*N*,*N*-diisopropylphosphoramidite (0.85 mL, 3.06 mmol) in 38% yield. Chromatography: hexane to hexane/EtOAc, 1:1.



111

$\underline{R_f}$: 0.36 (hexane/EtOAc, 1:1). IR (ATR): 1265 (P=O); 996 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.46 (s, 18H, $6CH_3$); 3.56-3.66 (m, 2H, $C\underline{H}_2OBn$); 3.83 (qt, *J* = 5.1, 1H, CH); 4.00-4.15 (m, 2H, CH_2OP); 4.54 (s, 2H, $PhC\underline{H}_2$); 4.59-4.67 (m, 2H, $PhC\underline{H}_2$); 7.25-7.37 (m, 10H, $10CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.9 ($3CH_3$); 30.0 ($3CH_3$); 66.1 (d, *J* = 6.4, CH_2OP); 69.8 ($\underline{C}H_2OBn$); 72.4 ($Ph\underline{C}H_2$); 73.5 ($Ph\underline{C}H_2$); 76.9 (d, *J* = 8.6, CH); 82.4 (d, *J* = 7.5, C); 82.5 (d, *J* = 7.4, C); 127.7 ($4CH_{Ar}$); 127.9 ($2CH_{Ar}$); 128.4 ($2CH_{Ar}$); 128.5 ($2CH_{Ar}$); 138.3, 138.5 ($2C_{Ar}$). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ -6.82. $[\alpha]_D^{20}$: +1.6 (c = 1.00, $CHCl_3$). MS (ESI, *m/z*): 487.1 $[M+Na]^+$.

Di-*tert*-butyl (2*R*)-2,3-dihydroxypropyl phosphate, 45. Following the general procedure 3, diol **45** was obtained from **111** (220 mg, 0.47 mmol) at 60ºC in quantitative yield.

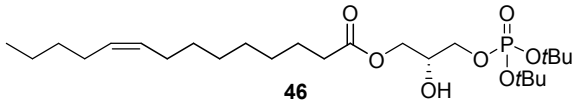


45

R_f: 0.06 (hexane/EtOAc, 1:1). IR (ATR): 3345 (O-H); 1025 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.47 (s, 18H, $6CH_3$); 3.60-3.73 (m, 2H, CH_2OH); 3.86-3.92 (m, 3H, CH, 2OH); 4.02 (dd, J = 9.1, 5.3, 2H, CH_2OP). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 30.1 ($3CH_3$); 30.2 ($3CH_3$); 63.7 (CH_2OH); 69.2 (d, J = 6.8, CH_2OP); 71.9 (d, J = 10.1, CH); 84.5 (d, J = 7.7, 2C). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ -6.03. $[\alpha]_D^{20}$: -1.5 (c = 1.70, methanol). MS (ESI, *m/z*): 307.1 $[M+Na]^+$.

4.3.3. Synthesis of intermediates 46-50

(2*R*)-3-[(Di-*tert*-butoxyphosphoryl)oxy]-2-hydroxypropyl (9*Z*)-tetradec-9-enoate, 46. Following the general procedure 15, ester **46** was obtained from myristoleic acid (24 µL, 95 µmol) and diol **45** (54 mg, 0.19 mmol) in 28% yield. Chromatography: DCM to DCM/methanol, 95:5.

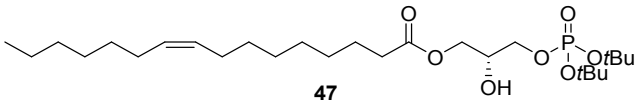


46

R_f: 0.88 (DCM/methanol, 95:5). IR (ATR): 3365 (O-H); 1739 (C=O); 1257 (P=O); 1000 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, J = 7.0, 3H, CH_3); 1.24-1.34 (m, 12H, $6CH_2$); 1.49 (s, 18H, $6CH_3$); 1.57-1.64 (m, 2H, CH_2CH_2CO); 1.94-2.02 (m, 4H, $2CH_2CH_{alkene}$); 2.33 (t, J = 7.6, 2H, CH_2CO); 3.95-4.13 (m, 3H, CH, CH_2OP); 4.15 (app d, J = 4.7, 2H, CO_2CH_2); 5.27-5.40 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3); 22.5, 25.0 ($2CH_2$); 27.1, 27.3 ($2CH_2CH_{alkene}$); 29.2, 29.23, 29.3, 29.8 ($4CH_2$); 29.9 ($3CH_3$); 30.0 ($3CH_3$); 32.1 (CH_2); 34.3 (CH_2CO); 64.7 (CO_2CH_2); 68.3 (d,

J = 5.8, CH$_2$OP); 69.1 (d, *J* = 5.0, CH); 83.4 (d, *J* = 7.5, 2C); 129.9, 130.1 (2CH$_{alkene}$); 173.9 (CO). ^{31}P-NMR (methanol-d_4, 121 MHz): δ -5.11. $[\alpha]_D^{20}$: +2.6 (c = 0.50, methanol). MS (ESI, *m/z*): 515.2 $[M+Na]^+$.

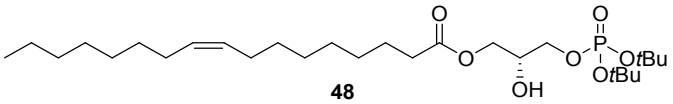
(2*R*)-3-[(Di-*tert*-butoxyphosphoryl)oxy]-2-hydroxypropyl (9*Z*)-hexadec-9-enoate, 47. Following the general procedure 15, ester **47** was obtained from palmitoleic acid (66 μL, 0.23 mmol) and diol **45** (133 mg, 0.47 mmol) in 49% yield. Chromatography: hexane/EtOAc, 40:1 to 1:1.



47

R_f: 0.38 (hexane/EtOAc, 1:1). IR (ATR): 3363 (O-H); 1739 (C=O); 1251 (P=O); 1000 (P-O). ^{1}H-NMR (CDCl$_3$, 300 MHz): δ 0.87 (t, *J* = 6.7, 3H, CH$_3$); 1.28 (m, 16H, 8CH$_2$); 1.48 (s, 18H, 6CH$_3$); 1.56-1.69 (m, 2H, CH$_2$CH$_2$CO); 1.96-2.00 (m, 4H, 2CH$_2$CH$_{alkene}$); 2.32 (t, *J* = 7.6, 2H, CH$_2$CO); 3.85 (br s, 1H, OH); 3.95-4.09 (m, 3H, CH, CH$_2$OP); 4.14 (app d, *J* = 4.6, 2H, CO$_2$CH$_2$); 5.27-5.38 (m, 2H, 2CH$_{alkene}$). ^{13}C-NMR (CDCl$_3$, 75 MHz): δ 14.2 (CH$_3$); 22.8, 25.0 (2CH$_2$); 27.3, 27.33 (2CH$_2$CH$_{alkene}$); 29.1 (CH$_2$); 29.2 (2CH$_2$); 29.3, 29.8, 29.84 (3CH$_2$); 29.9 (3CH$_3$); 30.0 (3CH$_3$); 31.9 (CH$_2$); 34.2 (CH$_2$CO); 64.7 (CO$_2$CH$_2$); 68.3 (d, *J* = 6.0, CH$_2$OP); 69.0 (d, *J* = 5.2, CH); 83.4 (d, *J* = 7.5, 2C); 129.9, 130.1 (2CH$_{alkene}$); 173.9 (CO). ^{31}P-NMR (CDCl$_3$, 121 MHz): δ -5.23. $[\alpha]_D^{20}$: -1.9 (c = 1.21, CHCl$_3$). MS (ESI, *m/z*): 543.3 $[M+Na]^+$.

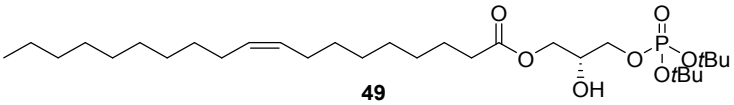
(2*R*)-3-[(Di-*tert*-butoxyphosphoryl)oxy]-2-hydroxypropyl (9*Z*)-heptadec-9-enoate, 48. Following the general procedure 15, ester **48** was obtained from carboxylic acid **42** (92 mg, 0.34 mmol) and diol **45** (195 mg, 0.69 mmol) in 40% yield. Chromatography: hexane/EtOAc, 20:1 to 2:1.



48

R_f: 0.36 (hexane/EtOAc, 1:1). IR (ATR): 3366 (O-H); 1739 (C=O); 1647 (C=C); 1259 (P=O); 1007 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.7, 3H, CH_3); 1.21-1.30 (m, 18H, $9CH_2$); 1.50 (s, 18H, $6CH_3$); 1.60-1.64 (m, 2H, CH_2CH_2CO); 1.97-2.01 (m, 4H, $2CH_2CH_{alkene}$); 2.34 (t, *J* = 7.6, 2H, CH_2CO); 3.71 (br s, 1H, OH); 3.98-4.11 (m, 3H, CH, CH_2OP); 4.16 (app d, *J* = 4.9, 2H, CO_2CH_2); 5.28-5.39 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3); 22.7, 24.9 ($2CH_2$); 27.2, 27.24 ($2CH_2CH_{alkene}$); 29.1 ($2CH_2$); 29.2, 29.25, 29.3 ($3CH_2$); 29.7 ($2CH_2$); 29.8 ($3CH_3$); 29.9 ($3CH_3$); 31.9 (CH_2); 34.1 (CH_2CO); 64.5 (CO_2CH_2); 68.3 (d, *J* = 5.4, CH_2OP); 69.1 (d, *J* = 4.8, CH); 83.3 (d, *J* = 7.8, 2C); 129.8, 130.0 ($2CH_{alkene}$); 173.8 (CO). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ -5.01. $[\alpha]_D^{20}$: +3.5 (c = 0.77, methanol). MS (ESI, *m/z*): 557.3 $[M+Na]^+$.

(2*R*)-3-[(di-*tert*-butoxyphosphoryl)oxy]-2-hydroxypropyl (9*Z*)-nonadec-9-enoate, 49. Following the general procedure 15, ester **49** was obtained from carboxylic acid **43** (73 mg, 0.25 mmol) and diol **45** (140 mg, 0.49 mmol) in 17% yield. Chromatography: hexane/EtOAc, 20:1 to 2:1.

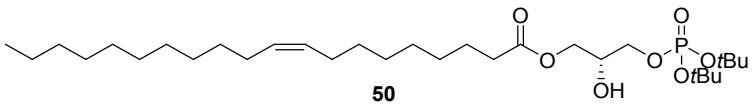


49

R_f: 0.37 (hexane/EtOAc, 1:1). IR (ATR): 3359 (O-H); 1738 (C=O); 1650 (C=C); 1252 (P=O); 1010 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, *J* = 6.7, 3H, CH_3); 1.26-1.29 (m, 22H, $11CH_2$); 1.49 (s, 18H, $6CH_3$); 1.59-1.64 (m, 2H, CH_2CH_2CO); 1.97-2.01 (m, 4H, $2CH_2CH_{alkene}$); 2.33 (t, *J* = 7.6, 2H, CH_2CO); 3.76 (br s, 1H, OH); 3.95-4.10 (m, 3H, CH, CH_2OP); 4.15 (app d, *J* = 4.9, 2H, CO_2CH_2); 5.28-5.39 (m, 2H, $2CH_{alkene}$). ^{13}C-

NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 22.8, 25.1 ($2CH_2$); 27.3, 27.4 ($2\underline{C}H_2CH_{alkene}$); 29.2 ($2CH_2$); 29.3, 29.4, 29.5, 29.7, 29.74, 29.8, 29.9 ($7CH_2$); 29.93 ($3CH_3$); 30.0 ($3CH_3$); 32.0 (CH_2); 34.1 ($\underline{C}H_2CO$); 64.7 ($CO_2\underline{C}H_2$); 68.3 (d, *J* = 6.0, CH_2OP); 69.1 (d, *J* = 5.0, CH); 83.4 (d, *J* = 7.5, 2C); 129.9, 130.1 ($2CH_{alkene}$); 173.9 (CO). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ -5.15. $[\alpha]_D^{20}$: -1.7 (c = 1.18, $CHCl_3$). MS (ESI, *m/z*): 449.4 [M-2*t*Bu+H]$^+$; 450.4 [M-2*t*Bu+2H]$^+$.

(2*R*)-3-[(Di-*tert*-butoxyphosphoryl)oxy]-2-hydroxypropyl (9*Z*)-icos-9-enoate, 50. Following the general procedure 15, ester **50** was obtained from carboxylic acid **44** (65 mg, 0.21 mmol) and diol **45** (121 mg, 0.42 mmol) in 12% yield. Chromatography: hexane/EtOAc, 20:1 to 2:1.



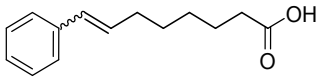
50

R_f: 0.43 (hexane/EtOAc, 1:1). IR (ATR): 3370 (O-H); 1740 (C=O); 1258 (P=O); 1000 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, *J* = 6.7, 3H, CH_3); 1.26-1.30 (m, 24H, $12CH_2$); 1.50 (s, 18H, $6CH_3$); 1.60-1.65 (m, 2H, $C\underline{H}_2CH_2CO$), 1.97-2.01 (m, 4H, $2C\underline{H}_2CH_{alkene}$); 2.33 (t, *J* = 7.6, 2H, CH_2CO); 3.72 (d, *J* = 4.1, 1H, OH); 3.98-4.11 (m, 3H, CH, CH_2OP); 4.16 (app d, *J* = 4.9, 2H, CO_2CH_2); 5.28-5.39 (m, 2H, $2CH_{alkene}$). ^{3}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 22.8, 25.0 ($2CH_2$); 27.3, 27.4 ($2\underline{C}H_2CH_{alkene}$); 29.2 ($2CH_2$); 29.3, 29.4, 29.5, 29.7, 29.78, 29.8, 29.84, 29.9 ($8CH_2$); 30.0 ($6CH_3$); 32.1 (CH_2); 34.3 ($\underline{C}H_2CO$); 64.7 ($CO_2\underline{C}H_2$); 68.4 (d, *J* = 5.5, CH_2OP); 69.2 (d, *J* = 4.6, CH); 83.4 (d, *J* = 7.2, 2C); 129.9, 130.2 ($2CH_{alkene}$); 173.9 (CO). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ -5.01. $[\alpha]_D^{20}$: +3.4 (c = 0.92, methanol). MS (MALDI, *m/z*): 599.4 [M+Na]$^+$.

4.4. Synthesis of intermediates 51-68 and final compound 17

4.4.1. Synthesis of acids 51-53

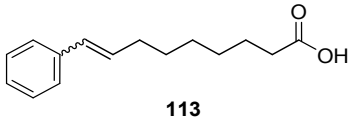
(7*E,Z*)-8-Phenyloct-7-enoic acid, 112. Following the general procedure 16, alkene **112** was obtained from 7-bromoheptanoic acid (441 mg, 2.11 mmol) and benzaldehyde (103 μL, 1.00 mmol) in 61% yield. Chromatography: hexane to hexane/EtOAc, 1:1.



112

R_f: 0.61 (hexane/EtOAc, 8:2). IR (ATR): 3024 (O-H); 1707 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): Mixture *E*:*Z* (2.3:1): δ 1.36-1.53 (m, 4H, $2CH_2$); 1.59-1.73 (m, 2H, CH_2); 2.23 (q, *J* = 6.8, 2H, $CH_2CH_{alkene(E)}$); 2.30-2.40 (m, 4H, $CH_2CH_{alkene(Z)}$, CH_2CO); 5.65 (dt, *J* = 11.7, 7.2, 1H, $CH_2CH_{alkene(Z)}$); 6.21 (dt, *J* = 15.8, 6.8, 1H, $CH_2CH_{alkene(E)}$); 6.39 (d, *J* = 15.6, 1H, $PhCH_{alkene(E)}$); 6.43 (d, *J* = 11.7, 1H, $PhCH_{alkene(Z)}$); 7.16-7.36 (m, 5H, $5CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): Mixture *E*:*Z* (2.3:1): δ 24.7 (CH_2); 28.5 ($CH_{2\ Z}$); 28.7 ($CH_{2\ E}$); 28.9 ($CH_{2\ Z}$); 29.1 ($CH_{2\ E}$); 32.9 (CH_2CH_{alkene}); 34.1 (CH_2CO); 126.1 ($2CH_{Ar\ E}$); 126.6 ($CH_{Ar\ Z}$); 127.0 ($CH_{Ar\ E}$); 128.3 ($2CH_{Ar\ Z}$); 128.6 ($2CH_{Ar\ E}$); 128.9 ($2CH_{Ar\ Z}$); 129.2 ($CH_{alkene(Z)}$); 130.2 ($CH_{alkene(E)}$); 130.8 ($CH_{alkene(E)}$); 132.8 ($CH_{alkene(Z)}$); 137.9 ($C_{Ar\ Z}$); 138.0 ($C_{Ar\ E}$); 179.9 (CO). MS (ESI, *m/z*): 217.1 $[M-H]^-$.

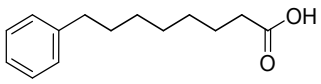
(8*E,Z*)-9-Phenylnon-8-enoic acid, 113. Following the general procedure 16, alkene **113** was obtained from 8-bromooctanoic acid (1g, 4.48 mmol) and benzaldehyde (0.36 mL, 3.58 mmol) in 70% yield. Chromatography: hexane to hexane/EtOAc, 1:1.



113

R_f: 0.52 (hexane/EtOAc, 8:2). IR (ATR): 3024 (O-H); 1706 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): Mixture *E*:*Z* (1.5:1): δ 1.33-1.41 (m, 4H, $2CH_2$); 1.45-1.52 (m, 2H, CH_2); 1.59-1.72 (m, 2H, CH_2); 2.22 (q, *J* = 6.9, 2H, $CH_2CH_{alkene(E)}$); 2.37 (app q, *J* = 7.6, 4H, $CH_2CH_{alkene(Z)}$, CH_2CO); 5.66 (dt, *J* = 11.7, 7.3, 1H, $CH_2CH_{alkene(Z)}$); 6.23 (dt, *J* = 15.8, 6.8, 1H, $CH_2CH_{alkene(E)}$); 6.39 (d, *J* = 15.5, 1H, $PhCH_{alkene(E)}$); 6.44 (d, *J* = 11.5, 1H, $PhCH_{alkene(Z)}$); 7.17-7.37 (m, 5H, $5CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): Mixture *E*:*Z* (1.5:1): δ 24.7 and 24.75 ($CH_{2\ E,\ Z}$); 28.6, 28.9, 29.0, 29.3 and 29.9 ($3CH_{2\ Z,E}$); 33.1 (CH_2CH_{alkene}); 34.1 and 34.14 ($CH_2CO_{\ E,\ Z}$); 126.0 ($2CH_{Ar\ E}$); 126.6 ($CH_{Ar\ Z}$); 126.9 ($CH_{Ar\ E}$); 128.2 ($2CH_{Ar\ Z}$); 128.6 ($2CH_{Ar\ E}$); 128.9 ($2CH_{Ar\ Z}$); 129.0 ($CH_{alkene(Z)}$); 130.0 ($CH_{alkene(E)}$); 131.06 ($CH_{alkene(E)}$); 133.10 ($CH_{alkene(Z)}$); 137.9 ($C_{Ar\ Z}$); 138.0 ($C_{Ar\ E}$); 180.1 (CO). MS (ESI, *m/z*): 231.1 $[M-H]^-$.

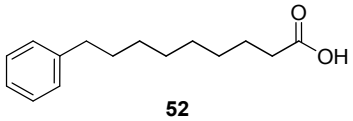
8-Phenyloctanoic acid, 51. Following the general procedure 3, carboxylic acid **51** was obtained from alkene **112** (60 mg, 0.27 mmol) at rt in 97% yield. The spectroscopic data correspond with those previously reported.[2]



51

R_f: 0.60 (hexane/EtOAc, 8:2). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.41 (app s, 6H, $3CH_2$); 1.70 (br s, 4H, $2CH_2$); 2.42 (t, *J* = 7.5, 2H, CH_2CO); 2.67 (t, *J* = 7.7, 2H, $PhCH_2$); 7.23-7.26 (m, 3H, $3CH_{Ar}$); 7.32-7.37 (m, 2H, $2CH_{Ar}$).

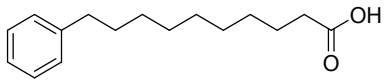
9-Phenylnonanoic acid, 52. Following the general procedure 3, carboxylic acid **52** was obtained from alkene **113** (300 mg, 1.29 mmol) at rt in 81% yield.



52

R_f: 0.61 (hexane/EtOAc, 8:2). IR (ATR): 3063 (O-H); 1707 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.32 (app s, 8H, $4CH_2$); 1.56-1.65 (m, 4H, $2CH_2$); 2.35 (t, *J* = 7.5, 2H, CH_2CO); 2.60 (t, *J* = 7.7, 2H, $PhCH_2$); 7.16-7.19 (m, 3H, $3CH_{Ar}$); 7.25-7.30 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.8, 29.2, 29.3, 29.35, 29.4, 31.6 ($6CH_2$); 34.2 (CH_2CO); 36.1 ($PhCH_2$); 125.7 (CH_{Ar}); 128.4 ($2CH_{Ar}$); 128.5 ($2CH_{Ar}$); 143.0 (C_{Ar}); 180.5 (CO). MS (ESI, *m/z*): 233.1 $[M-H]^-$.

10-Phenyldecanoic acid, 53. To a stirred solution of 10-phenyldecanol (500 mg, 2.10 mmol, 1 equiv) in dry DMF (2 mL), pyridinium dichromate (2.92 g, 3.89 mmol, 3.7 equiv) was added and the reaction was stirred at rt overnight. Then, solvent was evaporated under reduced pressure and the crude was purified by flash chromatography (DCM to DCM/methanol, 10:1) affording carboxylic acid **53** in 52% yield.

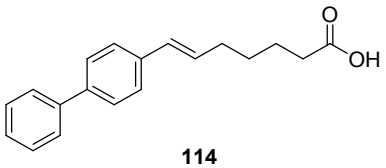


53

R_f: 0.6 (DCM/methanol, 9:1). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.32 (m, 10H, $5CH_2$); 1.63-1.65 (m, 4H, $2CH_2$); 2.34 (t, *J* = 7.4, 2H, CH_2CO); 2.60 (t, *J* = 7.5, 2H, $PhCH_2$); 7.18-7.22 (m, 3H, $3CH_{Ar}$); 7.27-7.33 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.8, 29.2, 29.4, 29.41, 29.5, 29.6, 31.6 ($7CH_2$); 34.2 (CH_2CO); 36.1 ($PhCH_2$); 125.7 (CH_{Ar}); 128.4 ($2CH_{Ar}$); 128.5 ($2CH_{Ar}$); 143.0 (C_{Ar}); 180.3 (CO).

4.4.2. Synthesis of acids 54-56

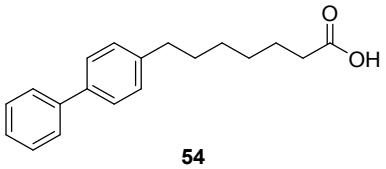
(6*E*)-7-([1,1'-Biphenyl]-4-yl)hept-6-enoic acid, 114. Following the general procedure 16, alkene **114** was obtained from 6-bromohexanoic acid (1 g, 5.13 mmol) and biphenyl-4-carbaldehyde (540 mg, 2.96 mmol) in 72% yield. Chromatography: DCM to dichoromethane/EtOAc, 5:1.



114

R_f: 0.39 (dichoromethane/EtOAc, 8:2). IR (ATR): 3026 (O-H); 1700 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.51-1.61 (m, 2H, CH_2); 1.67-1.78 (m, 2H, CH_2); 2.27 (q, J = 6.7, 2H, CH_2CH_{alkene}); 2.41 (t, J = 7.4, 2H, CH_2CO); 6.25 (dt, J = 15.8, 6.8, 1H, $CHCH_2$); 6.44 (d, J = 15.9, 1H, ArCH); 7.33 (t, J = 7.3, 1H, CH_{Ar}); 7.40-7.46 (m, 4H, $4CH_{Ar}$); 7.53-7.62 (m, 4H, $4CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.4; 28.9 ($2CH_2$); 32.8 (CH_2CH_{alkene}); 33.9 (CH_2CO); 126.5 ($2CH_{Ar}$); 127.0 ($2CH_{Ar}$); 127.30 (CH_{Ar}); 127.34 ($2CH_{Ar}$); 128.9 ($2CH_{Ar}$); 130.0; 130.5 ($2CH_{alkene}$); 136.9; 139.8; 141.0 ($3C_{Ar}$); 179.5 (CO). MS (ESI, *m/z*): 279.1 $[M-H]^-$.

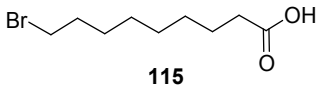
7-([1,1'-Biphenyl]-4-yl)heptanoic acid, 54. Following the general procedure 3, carboxylic acid **54** was obtained from alkene **114** (300 mg, 1.07 mmol) at rt as a white solid in 95% yield. The spectroscopic data correspond with those previously reported.[3]



54

R_f: 0.43 (DCM/EtOAc, 8:2). M.p.: 70-71ºC (lit.[3] m.p.: 69-70ºC). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.37-1.42 (m, 4H, $2CH_2$); 1.61-1.71 (m, 4H, $2CH_2$); 2.36 (t, J = 7.5, 2H, CH_2CO); 2.65 (t, J = 7.5, 2H, $ArCH_2$); 7.25 (d, J = 8.7, 2H, $2CH_{Ar}$); 7.32 (t, J = 7.3, 1H, CH_{Ar}); 7.43 (t, J = 7.4, 2H, $2CH_{Ar}$); 7.51 (d, J = 8.2, 2H, $2CH_{Ar}$); 7.56-7.60 (m, 2H, $2CH_{Ar}$). MS (ESI, *m/z*): 281.1 $[M-H]^-$.

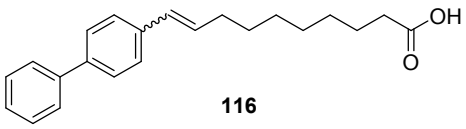
9-Bromononanoic acid, 115. Following the general procedure 19, carboxylic acid **115** was obtained from 9-bromononanol (1 g, 4.48 mmol) in 61% yield. Chromatography: DCM to DCM/EtOAc 5:1. The spectroscopic data correspond with those previously reported.[4]



115

R_f: 0.67 (DCM/EtOAc, 8:2). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.32-1.37 (m, 6H, $3CH_2$); 1.40-1.44 (m, 2H, CH_2); 1.58-1.69 (m, 2H, CH_2); 1.80-1.90 (m, 2H, CH_2); 2.36 (t, J = 7.5, 2H, CH_2CO); 3.40 (t, J = 6.8, 2H, CH_2Br); 8.81 (br s, 1H, OH).

(9*E,Z*)-10-([1,1'-Biphenyl]-4-yl)dec-9-enoic acid, 116. Following the general procedure 16, alkene **116** was obtained from **115** (650 mg, 5.13 mmol) and biphenyl-4-carbaldehyde (400 mg, 2.19 mmol) in 51% yield. Chromatography: DCM to DCM/EtOAc, 5:1.

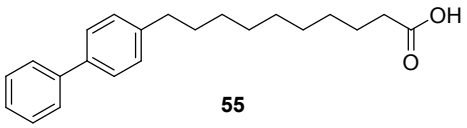


116

R_f: 0.5 (DCM/EtOAc, 8:2). IR (ATR): 3030 (O-H); 1705 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): Mixture *E*:*Z* (1.5:1): δ 1.36-1.39 (m, 6H, $3CH_2$); 1.48 (m, 2H, CH_2); 1.59-1.66 (m, 2H, CH_2); 2.23 (q, J = 6.7, 2H, $CH_2CH_{alkene(E)}$); 2.32-2.42 (m, 4H, $CH_2CH_{alkene(Z)}$, CH_2CO); 5.69 (dt, J = 11.8, 7.3, 1H, $CH_2CH_{alkene(Z)}$); 6.27 (dt, J = 15.8, 6.7, 1H, $CH_2CH_{alkene(E)}$); 6.42 (d, J = 15.9, 1H, $ArCH_{alkene(E)}$); 6.44 (d, J = 11.5, 1H, $ArCH_{alkene(Z)}$); 7.31-7.47 (m, 5H, $5CH_{Ar}$); 7.53-7.63 (m, 4H, $4CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): Mixture *E*:*Z* (1.5:1): δ 24.7 and 24.8 (CH_2); 28.9; 28.93; 29.0; 29.1; 29.2; 29.4 and 30.0 ($4CH_{2\ E,Z}$); 33.1 and 33.2 (CH_2CH_{alkene}); 34.2 (br s, CH_2CO); 126.4

($2CH_{Ar\ E}$); 126.9 ($2CH_{Ar\ Z}$); 127.0 ($2CH_{Ar\ E}$); 127.1 ($2CH_{Ar\ Z}$); 127.3 ($CH_{Ar\ E}$); 127.31 ($2CH_{Ar\ E}$); 128.5 ($CH_{Ar\ Z}$); 128.8 ($2CH_{Ar\ E}$); 128.9 ($2CH_{Ar\ Z}$); 129.3 ($2CH_{Ar\ Z}$); 129.5 ($CH_{alkene(Z)}$); 131.3 ($CH_{alkene(E)}$); 132.3 ($CH_{alkene(E)}$); 133.4 ($CH_{alkene(Z)}$); 137.0 and 137.1 (C_{Ar}); 139.3 and 139.6 (C_{Ar}); 140.9 and 141.0 (C_{Ar}); 180.3 (CO). MS (ESI, *m/z*): 321.1 $[M-H]^-$.

10-([1,1'-Biphenyl]-4-yl)decanoic acid, 55. Following the general procedure 3, carboxylic acid **116** was obtained from alkene **55** (240 mg, 0.75 mmol) at rt as a white solid in 83% yield.

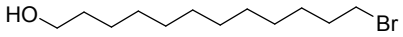


55

R_f: 0.5 (DCM/EtOAc, 8:2). M.p.: 92-95ºC. IR (ATR): 3032 (O-H); 1696 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.31-1.39 (m, 10H, $5CH_2$); 1.68 (m, 4H, $2CH_2$); 2.40 (t, *J* = 7.5, 2H, CH_2CO); 2.69 (t, *J* = 7.5, 2H, $ArCH_2$); 7.31 (d, *J* = 8.1, 2H, $2CH_{Ar}$); 7.37 (t, *J* = 7.3, 1H, CH_{Ar}); 7.48 (t, *J* = 7.5, 2H, $2CH_{Ar}$); 7.56 (d, *J* = 8.1, 2H, $2CH_{Ar}$); 7.62-7.65 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.8; 29.2; 29.3; 29.4; 29.5; 29.6; 31.6 ($7CH_2$); 34.2 (CH_2CO); 35.7 ($ArCH_2$); 127.1 (CH_{Ar}); 127.12 ($4CH_{Ar}$); 128.8 ($2CH_{Ar}$); 129.0 ($2CH_{Ar}$); 138.7; 141.3; 142.2 ($3C_{Ar}$), 180.2 (CO). MS (ESI, *m/z*): 323.3 $[M-H]^-$.

12-Bromododecan-1-ol, 117. To a suspension of 1,12-dodecanodiol (1.00 g, 4.94 mmol, 1 equiv) in cyclohexane (15 mL), 47% aq. HBr (15 mL) was added and the reaction was refluxed for 6 h. Then, the mixture was extracted with hexane and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was

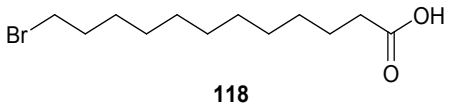
purified by flash cromatography (hexane to DCM) to afford bromoalcohol **117** as in 65% yield. The spectroscopic data correspond with those previously reported.[5]



117

R_f: 0.71 (DCM/EtOAc, 8:2). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27-1.44 (m, 16H, $8CH_2$); 1.52-1.61 (m, 2H, CH_2); 1.80-1.90 (m, 2H, CH_2); 3.40 (t, J = 6.9, 2H, CH_2Br); 3.64 (t, J = 6.6, 2H, CH_2OH).

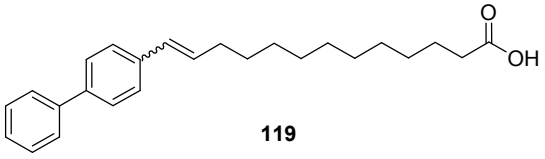
12-Bromododecanoic acid, 118. Following the general procedure 19, carboxylic acid **118** was obtained from bromoalcohol **117** (850 mg, 3.2 mmol) in 43% yield. Chromatography: DCM to DCM/EtOAc, 5:1. The spectroscopic data correspond with those previously reported.[5]



118

R_f: 0.51 (DCM/EtOAc, 8:2). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.28 (app s, 12H, $6CH_2$); 1.39-1.44 (m, 2H, CH_2); 1.58-1.65 (m, 2H, CH_2); 1.80-1.89 (m, 2H, CH_2); 2.35 (t, J = 7.5, 2H, CH_2CO); 3.40 (t, J = 6.8, 2H, CH_2Br).

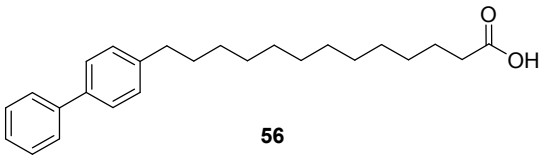
(12*E,Z*)- 13-([1,1'-Biphenyl]-4-yl)tridec-12-enoic acid, 119. Following the general procedure 16, alkene **119** was obtained from **118** (800 mg, 2.87 mmol) and biphenyl-4-carbaldehyde (422 mg, 2.32 mmol) in 38% yield. Chromatography: DCM to DCM/EtOAc, 5:1.



119

R_f: 0.46 (dichoromethane/EtOAc, 8:2). IR (ATR): 3030 (O-H); 1703 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): Mixture *E*:*Z* (1:1): δ 1.26-1.29 (m, 10H, $5CH_2$); 1.45-1.50 (m, 2H, CH_2); 1.60-1.66 (m, 4H, $2CH_2$); 2.23 (q, *J* = 6.9, 2H, $CH_2CH_{alkene(Z)}$); 2.32-2.39 (m, 4H, $CH_2CH_{alkene(E)}$, CH_2CO); 5.70 (dt, *J* = 11.7, 7.2, 1H, $CH_2CH_{alkene(Z)}$); 6.27 (dt, *J* = 15.8, 6.7, 1H, $CH_2CH_{alkene(E)}$); 6.43 (d, *J* = 11.6, 1H, $ArCH_{alkene(Z)}$); 6.47 (d, *J* = 15.2, 1H, $ArCH_{alkene(E)}$); 7.33-7.47 (m, 5H, $5CH_{Ar}$); 7.52-7.63 (m, 4H, $4CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): Mixture *E*:*Z* (1:1): δ 24.8 (CH_2); 28.9; 29.2; 29.4; 29.5; 29.53; 29.6; 29.7 and 30.1 ($7CH_{2\ Z,E}$); 31.7 and 33.3 (CH_2CH_{alkene}); 34.1 (CH_2CO); 126.4; 126.9; 127.0; 127.1; 127.2; 127.3; 128.4; 128.8 and 128.9 ($7CH_{Ar\ Z,E}$); 129.0 ($CH_{alkene\ Z/E}$); 129.3 ($2CH_{Ar\ Z/E}$); 129.4 ($CH_{alkene\ Z/E}$); 131.6 and 133.7 ($CH_{alkene\ Z,E}$); 137.0 and 137.2 (C_{Ar}); 138.8 and 139.3 (C_{Ar}); 140.2 and 141.0 (C_{Ar}); 179.7 (CO). MS (ESI, *m/z*): 363.2 $[M-H]^-$.

13-([1,1'-Biphenyl]-4-yl)tridecanoic acid, 56. Following the general procedure 3, carboxylic acid **56** was obtained from alkene **119** (300 mg, 0.82 mmol) at rt as a white solid in 96% yield.



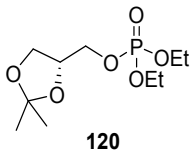
56

R_f: 0.46 (dichoromethane/EtOAc, 8:2). M.p.: 103-105ºC. IR (ATR): 3027 (O-H); 1696 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.22-1.46 (m, 16H, $8CH_2$); 1.57-1.73 (m, 4H, $2CH_2$); 2.35 (t, *J* = 7.5, 2H, CH_2CO); 2.65 (t, *J* = 7.5, 2H, $ArCH_2$); 7.26 (d, *J* = 8.0, 2H, $2CH_{Ar}$); 7.32 (t, *J* = 7.3, 1H, CH_{Ar}); 7.43 (t, *J* = 7.5, 2H, $2CH_{Ar}$); 7.52 (d, *J* = 8.1, 2H, $2CH_{Ar}$); 7.59 (d, *J* = 7.6, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.8; 29.2; 29.4; 29.5; 29.6; 29.7 ($6CH_2$); 29.72 ($2CH_2$); 29.8; 31.7 ($2CH_2$); 34.2 (CH_2CO); 35.8

(Ar$\underline{C}H_2$); 127.1 (CH_{Ar}); 127.12 ($4CH_{Ar}$); 128.8 ($2CH_{Ar}$); 129.0 ($2CH_{Ar}$); 138.7; 141.3; 142.3 ($3C_{Ar}$); 180.0 (CO). MS (ESI, *m/z*): 365.2 $[M-H]^-$.

4.4.3. Synthesis of phosphorylated diols 57, 58

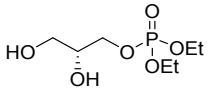
[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl diethyl phosphate, 120. To a solution of (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (0.3 mL, 2.43 mmol, 1 equiv) in anhydrous DCM (8 mL), diethyl chlorophosphate (0.44 mL, 3.04 mmol, 1.25 equiv) and potassium *tert*-butoxide (408 mg, 3.64 mmol, 1.5 equiv) were added and the mixture was stirred at rt for 48 h. Then, the reaction was quenched with a saturated aqueous solution of NH_4Cl (12 mL) and stirred for 10 additional min. The mixture was extracted with DCM and the organic phase was dried over Na_2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (DCM/EtOAc, 10:1 to 1:1), to afford pure product **120** in 92% yield.



120

$\underline{R_f}$: 0.26 (DCM/EtOAc, 8:2). IR (ATR): 1021 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.31 (td, *J* = 7.1, 0.9, 6H, $2CH_2C\underline{H_3}$); 1.33 (s, 3H, $CH_{3\ acetal}$); 1.39 (s, 3H, $CH_{3\ acetal}$); 3.81 (dd, *J* = 8.6, 5.5, 1H, ½CH_2O); 3.92-4.05 (m, 3H, ½CH_2O, CH_2OP); 4.07-4.16 (m, 4H, $2C\underline{H_2}CH_3$): 4.24-4.33 (m, 1H, CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 16.2 (d, *J* = 6.7, $2CH_2\underline{C}H_3$); 25.4 ($CH_{3\ acetal}$); 26.8 ($CH_{3\ acetal}$); 64.1 (d, *J* = 5.7, $2\underline{C}H_2CH_3$); 66.3 (CH_2O); 67.4 (d, *J* = 5.8, CH_2OP); 74.2 (d, *J* = 8.2, CH); 109.9 (C).

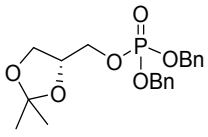
(2*R*)-2,3-Dihydroxypropyl diethyl phosphate, 57. Following the general procedure 8, diol **57** was obtained from **120** (600 mg, 2.24 mmol) in 50% yield. Chromatography: DCM/methanol, 50:1 to 10:1.



57

R_f: 0.11 (DCM/methanol, 10:1). IR (ATR): 3405 (O-H); 1256 (P=O); 1027 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.34 (t, *J* = 7.1, 6H, $2CH_3$); 3.21 (br s, 2H, 2OH); 3.60-3.73 (m, 2H, CH_2OH); 3.75-3.83 (m, 1H, ½CH_2OP); 3.86-3.94 (m, 1H, CH); 4.06-4.18 (m, 5H, ½CH_2OP, 2CH_2CH_3). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 16.2 (d, *J* = 6.7, $2CH_3$); 62.9 (CH_2OH); 64.5 (d, *J* = 6.0, 2CH_2CH_3); 68.5 (d, *J* = 5.8, CH_2OP); 70.8 (d, *J* = 5.5, CH). $[\alpha]_D^{20}$: -6.5 (c = 1.11, methanol).

Dibenzyl [(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl phosphate, 121. Following the general procedure 14, compound **121** was obtained from (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (0.2 mL, 1.62 mmol) and dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.97 mL, 2.91 mmol) in 76% yield. Chromatography: hexane to hexane/EtOAc, 1:1.

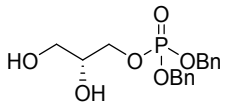


121

R_f: 0.4 (hexane/EtOAc, 1:1). IR (ATR): 1255 (P=O); 991 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H, CH_3); 1.38 (s, 3H, CH_3); 3.72 (dd, *J* = 8.6, 5.5, 1H, ½CH_2O); 3.87-4.04 (m, 3H, ½CH_2O, CH_2OP); 4.20 (qt, *J* = 5.7, 1H, CH); 4.97-5.13 (m, 4H, 2PhCH_2); 7.34 (app s, 10H, $10CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.3, 26.8 ($2CH_3$);

66.2 (CH_2O); 67.5 (d, J = 5.9, CH_2OP); 69.5 (d, J = 5.6, 2Ph$\underline{C}H_2$); 74.0 (d, J = 8.3, CH); 109.9 (C); 128.1 (4CH_{Ar}); 128.7 (6CH_{Ar}); 135.8 (d, J = 6.6, 2C_{Ar}). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ 2.03. $[\alpha]_D^{20}$: +1.6 (c = 1.00, methanol). MS (ESI, *m/z*): 393.1 $[M+H]^+$.

Dibenzyl (2*R*)-2,3-dihydroxypropyl phosphate, 58. Following the general procedure 8, diol **58** was obtained from **121** (390 mg, 0.99 mmol) in 65% yield. Chromatography: EtOAc to EtOAc/ethanol, 7:3.

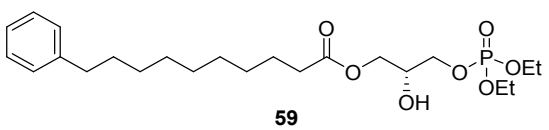


58

R_f: 0.56 (EtOAc). IR (ATR): 3368 (O-H); 1255 (P=O); 1013 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.53 (br s, 2H, OH); 3.52-3.65 (m, 2H, CH_2OH); 3.78-3.85 (m, 1H, CH); 4.03 (dd, J = 9.5, 5.0, 2H, CH_2OP); 4.98-5.11 (m, 4H, 2PhCH_2); 7.35 (app s, 10H, 10CH_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 62.7 (CH_2OH); 68.8 (d, J = 5.9, CH_2OP); 69.9 (d, J = 5.8, 2PhCH_2); 70.7 (d, J = 5.2, CH); 128.2 (4CH_{Ar}); 128.8 (4CH_{Ar}); 128.9 (2CH_{Ar}); 135.60 (d, J = 6.6, 2C_{Ar}). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ 3.19. $[\alpha]_D^{20}$: -4.6 (c = 0.99, methanol). MS (ESI, *m/z*): 353.0 $[M+H]^+$.

4.4.4. Synthesis of intermediates 59-68 and final compound 17

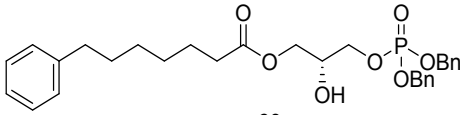
(2*R*)-3-[(Diethoxyphosphoryl)oxy]-2-hydroxypropyl 10-phenyldecanoate, 59. Following the general procedure 15, ester **59** was obtained from carboxylic acid **53** (136 mg, 0.55 mmol) and diol **57** (250 mg, 1.10 mmol) in 30% yield. Chromatography: DCM/methanol, 200:1 to 50:1.



59

R_f: 0.45 (DCM/methanol, 10:1). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.28 (app s, 10H, $5CH_2$); 1.35 (td, J = 7.1, 0.9, 6H, $2CH_3$); 1.55-1.62 (m, 4H, $2CH_2$); 2.33 (t, J = 7.6, 2H, CH_2CO); 2.59 (t, J = 7.7, 2H, $PhCH_2$); 4.02-4.26 (m, 9H, CH, $2CH_2CH_3$, CH_2OP, CO_2CH_2); 7.14-7.18 (m, 3H, $3CH_{Ar}$); 7.24-7.30 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 16.2 (d, J = 6.6, $2CH_3$); 25.0, 29.2, 29.4, 29.41, 29.5, 29.6, 31.6 ($7CH_2$); 34.2 (CH_2CO); 36.1 ($PhCH_2$); 64.44 (d, J = 5.4, CH_2CH_3); 64.45 (d, J = 5.4, CH_2CH_3); 64.5 (CO_2CH_2); 68.8 (d, J = 5.7, CH_2OP); 69.0 (d, J = 5.5, CH); 125.7 (CH_{Ar}); 128.3 ($2CH_{Ar}$); 128.5 ($2CH_{Ar}$); 143.0 (C_{Ar}); 174.0 (CO). MS (ESI, *m/z*): 459.2 $[M+H]^+$.

(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 7-phenylheptanoate, 60. Following the general procedure 15, ester **60** was obtained from 7-phenylheptanoic acid (35 mg, 0.17 mmol) and diol **58** (120 mg, 0.34 mmol) in 39% yield. Chromatography: DCM/EtOAc, 100:1 to 7:3.

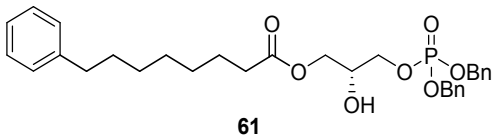


60

R_f: 0.32 (DCM/EtOAc, 8:2). IR (ATR): 3384 (O-H); 1736 (C=O); 1253 (P=O); 1007 (P-O). ^{1}H-NMR (C_6D_6, 300 MHz): δ 1.22-1.27 (m, 4H, $2CH_2$); 1.53-1.63 (m, 4H, $2CH_2$); 2.20 (t, J = 7.5, 2H, CH_2CO); 2.57 (t, J = 7.5, 2H, $PhCH_2$); 4.11-4.21 (m, 3H, CH, CH_2OP); 4.27-4.38 (m, 2H, CO_2CH_2); 4.47 (br s, 1H, OH); 5.00-5.14 (m, 4H, $2OCH_2Ph$); 7.13-7.24 (m, 9H, $9CH_{Ar}$); 7.29-7.35 (m, 6H, $6CH_{Ar}$). ^{13}C-NMR (C_6D_6, 75 MHz): δ 25.1; 29.2; 29.22; 31.6 ($4CH_2$); 34.1 (CH_2CO); 36.2 ($PhCH_2$); 64.6 (CO_2CH_2); 69.0 (d, J = 5.5, CH); 69.4 (d, J = 5.8, CH_2OP); 69.7 (d, J = 4.9, OCH_2Ph); 69.74 (d, J = 5.1, OCH_2Ph); 126.0 (CH_{Ar}); 128.4 ($2CH_{Ar}$); 128.41 ($2CH_{Ar}$); 128.6 ($2CH_{Ar}$); 128.7 ($2CH_{Ar}$); 128.76 ($2CH_{Ar}$); 128.78 ($4CH_{Ar}$); 136.4 (d, J = 6.7, $2C_{Ar}$); 142.9 (C_{Ar}); 173.1

(CO). ^{31}P-NMR (C_6D_6, 121 MHz): δ 3.65. MS (ESI, *m/z*): 523.2 $[M\text{-}H_2O+H]^+$; 541.3 $[M+H]^+$.

(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 8-phenyloctanoate, 61. Following the general procedure 15, ester **61** was obtained from carboxylic acid **51** (37 mg, 0.17 mmol) and diol **58** (120 mg, 0.34 mmol) in 53% yield. Chromatography: DCM to DCM/methanol, 95:5.

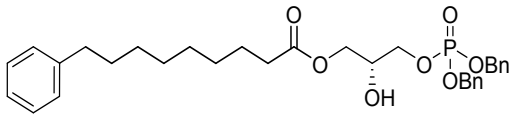


61

R_f: 0.44 (DCM/methanol, 95:5). IR (ATR): 3382 (O-H); 1738 (C=O); 1265 (P=O); 1016 (P-O). ^{1}H-NMR (methanol-d_4, 300 MHz): δ 1.22-1.35 (m, 6H, $3CH_2$); 1.48-1.64 (m, 4H, $2CH_2$); 2.19-2.32 (m, 2H, CH_2CO); 2.52-2.59 (m, 2H, $PhCH_2$); 3.42-4.70 (m, 1H, ½CH_2OP); 3.91-4.36 (m, 4H, CH, ½CH_2OP, CO_2CH_2); 5.01-5.10 (m, 4H, $2OCH_2Ph$); 7.09-7.14 (m, 3H, $3CH_{Ar}$); 7.20-7.25 (m, 2H, $2CH_{Ar}$); 7.30-7.39 (m, 10H, $10CH_{Ar}$). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 26.0, 30.07, 30.1, 30.2, 32.6 ($5CH_2$); 34.7 (CH_2CO); 36.9 ($PhCH_2$); 65.4 (CO_2CH_2); 68.9 (d, *J* = 7.9, CH); 69.5 (d, *J* = 6.1, CH_2OP); 70.9 (d, *J* = 5.9, $2OCH_2Ph$); 126.6 (CH_{Ar}); 129.2 ($2CH_{Ar}$); 129.24 ($2CH_{Ar}$); 129.4 ($4CH_{Ar}$); 129.7 ($4CH_{Ar}$); 129.8 ($2CH_{Ar}$); 137.1 (d, *J* = 6.4, $2C_{Ar}$); 143.9 (C_{Ar}); 175.1 (CO). ^{31}P-NMR (methanol-d_4, 121 MHz): δ 1.54. $[\alpha]_D^{20}$: +1.6 (c = 1.19, methanol). MS (ESI, *m/z*): 537.2 $[M\text{-}H_2O+H]^+$; 555.2 $[M+H]^+$.

(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 9-phenylnonanoate, 62. Following the general procedure 15, ester **62** was obtained from carboxylic acid **52**

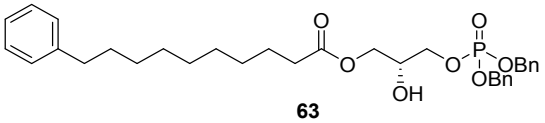
(90 mg, 0.38 mmol) and diol **58** (271 mg, 0.76 mmol) in 58% yield. Chromatography: DCM to DCM/methanol, 95:5.



62

R_f: 0.44 (DCM/methanol, 95:5). IR (ATR): 3325 (O-H); 1736 (C=O); 1245 (P=O); 1013 (P-O). ^{1}H-NMR (methanol-d_4, 300 MHz): δ 1.25-1.35 (m, 8H, 4CH_2); 1.55-1.64 (m, 4H, 2CH_2); 2.30 (t, J = 7.4, 2H, CH_2CO); 2.58 (t, J = 7.7, 2H, PhCH_2); 3.91-3.98 (m, 1H, CH); 3.98-4.03 (m, 2H, CH_2OP); 4.07 (dd, J = 5.1, 1.5, 2H, CO_2CH_2); 5.05 (s, 2H, OCH_2Ph); 5.08 (s, 2H, OCH_2Ph); 7.10-7.16 (m, 3H, 3CH_{Ar}); 7.21-7.26 (m, 2H, 2CH_{Ar}); 7.36 (app s, 10H, 10CH_{Ar}). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 26.8, 30.1, 30.2, 30.3, 30.4, 32.7 (6CH_2); 34.9 (CH_2CO); 36.9 (PhCH_2); 65.4 (CO_2CH_2); 68.9 (d, J = 8.0, CH); 69.6 (d, J = 6.4, CH_2OP); 70.9 (d, J = 5.8, 2OCH_2Ph); 126.6 (CH_{Ar}); 129.20 (4CH_{Ar}); 129.24 (2CH_{Ar}); 129.4 (2CH_{Ar}); 129.7 (4CH_{Ar}); 129.8 (2CH_{Ar}); 137.2 (d, J = 6.5, 2C_{Ar}); 144.0 (C_{Ar}); 175.2 (CO). ^{31}P-NMR (methanol-d_4, 121 MHz): δ 1.61. $[\alpha]_D^{20}$: +0.02 (c = 0.65, methanol). MS (ESI, *m/z*): 551.2 [M-H_2O+H]$^+$; 569.3 [M+H]$^+$.

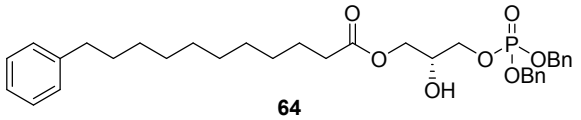
(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 10-phenyl decanoate, 63. Following the general procedure 15, ester **63** was obtained from carboxylic acid **53** (82 mg, 0.33 mmol) and diol **58** (233 mg, 0.66 mmol) in 16% yield. Chromatography: DCM/EtOAc, 100:1 to 1:1.



63

R_f: 0.43 (DCM/EtOAc, 8:2). IR (ATR): 1738 (C=O); 1022 (P-O). ^{1}H-NMR (C_6D_6, 300 MHz): δ 1.15-1.20 (m, 10H, 5CH_2); 1.49-1.58 (m, 4H, 2CH_2); 2.11 (t, *J* = 7.5, 2H, CH_2CO); 2.51 (t, *J* = 7.5, 2H, PhCH_2); 3.95-4.06 (m, 3H, CH, CH_2OP); 4.12-4.24 (m, 2H, CO_2CH_2); 4.86-5.00 (m, 4H, 2OCH_2Ph); 7.03-7.12 (m, 9H, 9CH_{Ar}); 7.16-7.22 (m, 6H, 6CH_{Ar}). ^{13}C-NMR (C_6D_6, 75 MHz): δ 25.2, 29.4, 29.6, 29.7, 29.8, 29.9, 31.9 (7CH_2); 34.2 (CH_2CO); 36.4 (PhCH_2); 64.6 (CO_2CH_2); 69.0 (d, *J* = 5.4, CH); 69.4 (d, *J* = 5.9, CH_2OP); 69.7 (d, *J* = 5.0, OCH_2Ph); 69.8 (d, *J* = 5.1, OCH_2Ph); 126.0 (CH_{Ar}); 128.5 (2CH_{Ar}); 128.6 (2CH_{Ar}); 128.8 (2CH_{Ar}); 128.83 (2CH_{Ar}); 128.9 (6CH_{Ar}); 136.4 (d, *J* = 6.7, 2C_{Ar}), 143.0 (C_{Ar}); 173.2 (CO). ^{31}P-NMR (C_6D_6, 121 MHz): δ 3.92. MS (ESI, *m/z*): 565.2 $[M-H_2O+H]^+$; 583.3 $[M+H]^+$.

(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 11-phenyl undecanoate, 64. Following the general procedure 15, ester **64** was obtained from 11-phenylundecanoic acid (37 mg, 0.14 mmol) and diol **58** (99 mg, 0.28 mmol) in 18% yield. Chromatography: hexane to hexane/EtOAc, 7:3.

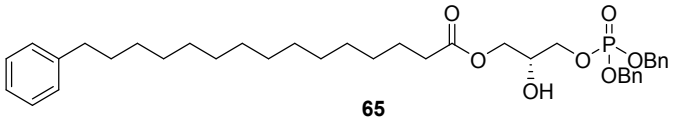


64

R_f: 0.28 (hexane/EtOAc, 6:4). ^{1}H-NMR (methanol-d_4, 300 MHz): δ 1.19-1.36 (m, 12H, 6CH_2); 1.49-1.65 (m, 4H, 2CH_2); 2.19-2.37 (m, 2H, CH_2CO); 2.58 (t, *J* = 7.6, 2H, PhCH_2); 3.62-4.18 (m, 5H, CH, CH_2OP, CO_2CH_2); 4.97-5.12 (m, 4H, 2OCH_2Ph); 7.10-7.16 (m, 3H, 3CH_{Ar}); 7.21-7.26 (m, H, 2CH_{Ar}); 7.28-7.41 (app s, 10H, 10 CH_{Ar}). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 25.9, 30.2, 30.28, 30.34 (4CH_2); 30.5 (2CH_2); 30.6, 32.8 (2CH_2); 34.8 (CH_2CO); 36.9 (PhCH_2); 65.4 (CO_2CH_2); 68.9 (d, *J* = 8.0, CH); 69.5 (d, *J* = 6.0, CH_2OP); 70.9 (d, *J* = 5.9, 2OCH_2Ph); 126.6 (CH_{Ar}); 129.2 (2CH_{Ar}); 129.23

(4CH_{Ar}); 129.4 (4CH_{Ar}); 129.7 (2CH_{Ar}); 129.8 (2CH_{Ar}); 137.1 (d, *J* = 6.1, 2C_{Ar}), 144.0 (C_{Ar}); 175.1 (CO). ^{31}P-NMR (methanol-d_4, 121 MHz): δ 1.61.

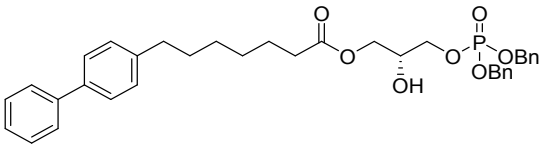
(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 15-phenyl pentadecanoate, 65. Following the general procedure 15, ester **65** was obtained from 15-phenylpentadecanoic acid (80 mg, 0.25 mmol) and diol **58** (177 mg, 0.50 mmol) in 18% yield. Chromatography: DCM/EtOAc, 100:1 to 1:1.



65

R_f: 0.55 (DCM/EtOAc, 8:2). IR (ATR): 3334 (O-H); 1740 (C=O); 1259 (P=O); 1017 (P-O). ^{1}H-NMR (C_6D_6, 500 MHz): δ 1.20-1.36 (m, 20H, 10CH_2); 1.54-1.58 (m, 4H, 2CH_2); 2.10 (t, *J* = 7.5, 2H, CH_2CO); 2.52 (t, *J* = 7.5, 2H, PhCH_2); 3.84-3.89 (m, 1H, CH); 3.91-3.99 (m, 2H, CH_2OP); 4.07 (dd, *J* = 11.4, 5.3, 1H, ½CO_2CH_2); 4.11 (dd, *J* = 11.4, 5.7, 1H, ½CO_2CH_2); 4.85-4.96 (m, 4H, 2OCH_2Ph); 7.04-7.12 (m, 8H, 8CH_{Ar}); 7.15-7.22 (m, 7H, 7CH_{Ar}). ^{13}C-NMR (C_6D_6, 125 MHz): δ 25.3, 29.5, 29.7, 29.72, 29.9, 30.0, 30.08, 30.1, 30.14 (9CH_2); 30.2 (2CH_2); 32.0 (CH_2); 34.2 (CH_2CO); 36.4 (PhCH_2); 64.5 (CO_2CH_2); 69.2 (d, *J* = 4.8, CH); 69.4 (d, *J* = 5.6, CH_2OP); 69.7 (d, *J* = 5.5, OCH_2Ph); 69.74 (d, *J* = 5.5, OCH_2Ph); 126.2 (CH_{Ar}); 128.5 (4CH_{Ar}); 128.54 (2CH_{Ar}); 128.8 (2CH_{Ar}); 128.84 (2CH_{Ar}); 128.9 (4CH_{Ar}); 136.4 (d, *J* = 6.5, 2C_{Ar}); 143.1 (C_{Ar}); 173.1 (CO). ^{31}P-NMR (C_6D_6, 121 MHz): δ 4.60. MS (ESI, *m/z*): 653.4 $[M+H]^+$.

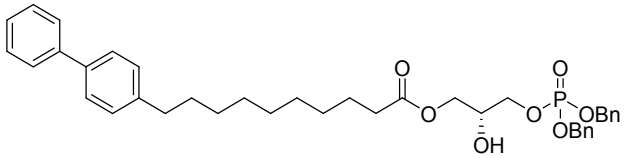
(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 7-([1,1'-biphenyl]-4-yl)heptanoate, 66. Following the general procedure 15, ester **66** was obtained from carboxylic acid **54** (100 mg, 0.35 mmol) and diol **58** (249 mg, 0.71 mmol) in 17% yield. Chromatography: DCM/EtOAc, 100:1 to 1:1.



66

R_f: 0.54 (DCM/EtOAc, 8:2). IR (ATR): 3385 (O-H); 1736 (C=O); 1259 (P=O); 1017 (P-O). ^{1}H-NMR (C_6D_6, 300 MHz): δ 1.25-1.29 (m, 4H, $2CH_2$); 1.58-1.64 (m, 4H, $2CH_2$); 2.21 (t, *J* = 7.5, 2H, CH_2CO); 2.59 (t, *J* = 7.5, 2H, $ArCH_2$); 4.11-4.19 (m, 3H, CH, CH_2OP); 4.25-4.36 (m, 2H, CO_2CH_2); 4.41 (br s, 1H, OH); 4.97-5.11 (m, 4H, $2OCH_2Ph$); 7.11-7.37 (m, 15H, $15CH_{Ar}$); 7.58-7.65 (m, 4H, $4CH_{Ar}$). ^{13}C-NMR (C_6D_6, 75 MHz): δ 25.1; 29.16; 29.2; 31.6 ($4CH_2$); 34.1 (CH_2CO); 35.8 ($ArCH_2$); 64.6 (CO_2CH_2); 68.9 (d, *J* = 5.6, CH); 69.3 (d, *J* = 5.7, CH_2OP); 69.6 (d, *J* = 4.9, OCH_2Ph); 69.7 (d, *J* = 5.1, OCH_2Ph); 127.2 (CH_{Ar}); 127.3 ($2CH_{Ar}$); 127.4 ($2CH_{Ar}$); 128.3 ($2CH_{Ar}$); 128.5 ($2CH_{Ar}$); 128.6 ($2CH_{Ar}$); 128.7 ($4CH_{Ar}$); 129.0 ($2CH_{Ar}$); 129.2 ($2CH_{Ar}$); 136.3 (d, *J* = 6.7, $2C_{Ar}$); 139.2; 141.7; 142.0 ($3C_{Ar}$); 173.1 (CO). ^{31}P-NMR (C_6D_6, 121 MHz): δ 3.77. MS (ESI, *m/z*): 599.7 $[M-H_2O+H]^+$; 617.7 $[M+H]^+$.

(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 10-([1,1'-biphenyl]-4-yl)decanoate, 67. Following the general procedure 15, ester **67** was obtained from carboxylic acid **55** (92 mg, 0.28 mmol) and diol **58** (200 mg, 0.57 mmol) in 24% yield. Chromatography: DCM to DCM/EtOAc, 6:4.

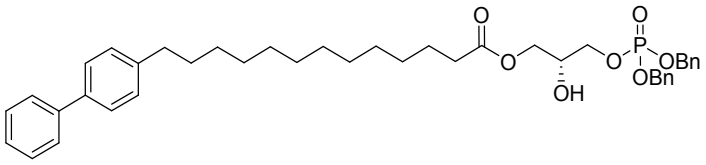


67

R_f: 0.51 (DCM/EtOAc, 8:2). IR (ATR): 3384 (O-H); 1738 (C=O); 1259 (P=O); 1016 (P-O). ^{1}H-NMR (C_6D_6, 300 MHz): δ 1.17-1.24 (m, 10H, $5CH_2$); 1.54-1.62 (m, 4H,

$2CH_2$); 2.12 (t, *J* = 7.4, 2H, CH_2CO); 2.51-2.58 (m, 2H, Ar$\underline{C}H_2$); 4.00-4.07 (m, 3H, CH, CH_2OP); 4.13-4.24 (m, 3H, CO_2CH_2, OH); 4.86-5.00 (m, 4H, 2O$\underline{C}H_2$Ph); 7.01-7.26 (m, 15H, $15CH_{Ar}$); 7.48-7.54 (m, 4H, $4CH_{Ar}$). ^{13}C-NMR (C_6D_6, 75 MHz): δ 25.2; 29.5; 29.6; 29.7; 29.8; 29.9; 31.9 ($7CH_2$); 34.2 ($\underline{C}H_2CO$); 36.0 (Ar$\underline{C}H_2$); 64.6 ($CO_2\underline{C}H_2$); 69.0 (d, *J* = 5.4, CH); 69.4 (d, *J* = 5.9, CH_2OP); 69.7 (d, *J* = 5.0, O$\underline{C}H_2$Ph); 69.74 (d, *J* = 5.0, O$\underline{C}H_2$Ph); 127.3 (CH_{Ar}); 127.4 ($2CH_{Ar}$); 127.5 ($2CH_{Ar}$); 128.4 ($2CH_{Ar}$); 128.42 ($2CH_{Ar}$); 128.7 ($2CH_{Ar}$); 128.8 ($4CH_{Ar}$); 129.1 ($2CH_{Ar}$); 129.3 ($2CH_{Ar}$); 136.4 (d, *J* = 6.7, $2C_{Ar}$,); 139.3; 141.7; 142.1 ($3C_{Ar}$); 173.2 (CO). ^{31}P-NMR (C_6D_6, 121 MHz): δ 3.93. $[\alpha]_D^{20}$: +0.7 (c = 1.5, methanol). MS (ESI, *m/z*): 641.7 $[M-H_2O+H]^+$; 659.7 $[M+H]^+$.

(2*R*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-hydroxypropyl 13-([1,1'-biphenyl]-4-yl)tridecanoate, 68. Following the general procedure 15, ester **68** was obtained from carboxylic acid **56** (104 mg, 0.28 mmol) and diol **58** (200 mg, 0.57 mmol) in 10% yield. Chromatography: DCM/EtOAc, 100:1 to 1:1.

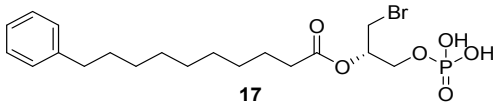


68

R_f: 0.42 (DCM/EtOAc, 8:2). IR (ATR): 1738 (C=O); 1260 (P=O); 1018 (P-O). ^{1}H-NMR (C_6D_6, 300 MHz): δ 1.14-1.30 (m, 16H, $8CH_2$); 1.54-1.64 (m, 4H, $2CH_2$); 2.11 (t, *J* = 7.5, 2H, CH_2CO); 2.57 (t, *J* = 7.5, 2H, Ar$\underline{C}H_2$); 3.92 (br s, 2H, CH, OH); 3.99 (dd, *J* = 10.0, 3.3, 2H, CH_2OP); 4.15 (AB system, *J* = 11.3, 4.5, 2H, CO_2CH_2); 4.84-5.00 (m, 4H, $2OCH_2Ph$); 7.03-7.27 (m, 15H, $15CH_{Ar}$); 7.48-7.55 (m, 4H, $4CH_{Ar}$). ^{13}C-NMR (C_6D_6, 75 MHz): δ 25.3; 29.5 ($2CH_2$); 29.7 ($2CH_2$); 29.9; 30.0 ($2CH_2$); 30.1 ($2CH_2$); 30.13; 32.0 ($2CH_2$); 34.2 ($\underline{C}H_2CO$); 36.0 (Ar$\underline{C}H_2$); 64.6 ($CO_2\underline{C}H_2$); 69.1 (d, *J* = 5.0,

CH); 69.4 (d, *J* = 5.8, CH_2OP); 69.7 (d, *J* = 5.0, O<u>C</u>H_2Ph); 69.74 (d, *J* = 5.1, O<u>C</u>H_2Ph); 127.3 (CH_{Ar}); 127.4 ($2CH_{Ar}$); 127.5 ($2CH_{Ar}$); 128.4 ($2CH_{Ar}$); 128.41 ($2CH_{Ar}$); 128.7 ($2CH_{Ar}$); 128.8 ($4CH_{Ar}$); 129.1 ($2CH_{Ar}$); 129.3 ($2CH_{Ar}$); 136.4 (d, *J* = 6.8, $2C_{Ar}$); 139.3; 141.8; 142.1 ($3C_{Ar}$); 173.1 (CO). <u>^{31}P-NMR (C_6D_6, 121 MHz)</u>: δ 4.61.<u>MS (ESI, *m/z*)</u>: 683.4 $[M\text{-}H_2O+H]^+$; 701.4 $[M+H]^+$.

(2*S*)-1-Bromo-3-(phosphonooxy)propan-2-yl 10-phenyldecanoate, 17. Thoroughly dried diethyl phosphate **59** (76 mg, 0.17 mmol, 1 equiv) was dissolved in anhydrous DCM (2 mL) and TMSBr (0.22 mL, 1.66 mmol, 10 equiv) was added dropwise at rt. The reaction mixture was stirred for 4 h at rt, after which the solvent was evaporated at reduced pressure and the crude was dissolved in 95% methanol in water (5 mL) and stirred for an additional hour. The mixture was then filtered through a short pad of Celite and concentrated to afford compound **17** in 90% yield. The spectroscopic data were consistent with those obtained for enantiomer **(*S*)-17**, and the specific rotation value agrees with that determined for **(*S*)-17**, confirming the *S* configuration of the chiral center. $[\alpha]_D^{20}$: +4.9 (c = 0.50, methanol).



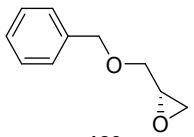
17

4.5. Synthesis of final compounds 69-72

4.5.1. Synthesis of alcohol 122

(2*S*)-2-[(Benzyloxy)methyl]oxirane, 123. To a suspension of NaH (65 mg, 1.62 mmol, 1.2 equiv, 60% dispersion in oil) in anhydrous DMF (3 mL) at 0ºC, (2*R*)-oxiran-2-ylmethanol (100 mg, 1.35 mmol, 1 equiv) was added, followed by benzyl bromide

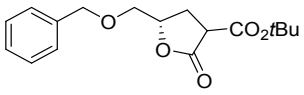
(0.21 mL, 1.76 mmol, 1.3 equiv). The reaction was allowed to warm up to rt and stirred overnight. Afterward, water was added and the mixture was extracted with DCM. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford product **123** in quantitative yield, which was used in the next step without further purification. Spectroscopic data correspond with those previously reported.[6]



123

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.62 (dd, *J* = 5.0, 2.7, 1H, ½$CH_{2\ epox}$); 2.81 (dd, *J* = 4.9, 4.1, 1H, ½$CH_{2\ epox}$); 3.17-3.22 (m, 1H, CH); 3.45 (dd, *J* = 11.4, 5.8, 1H, ½CH_2O); 3.77 (dd, *J* = 11.4, 3.0, 1H, ½CH_2O); 4.56 (d, *J* = 11.9, 1H, ½OCH_2Ph); 4.62 (d, *J* = 11.9, 1H, ½OCH_2Ph); 7.27-7.39 (m, 5H, 5CH_{Ar}).

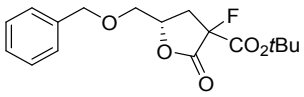
***tert*-Butyl (5*S*)-5-((benzyloxy)methyl)-2-oxotetrahydrofuran-3-carboxylate, 124.** Di-*tert*-butyl malonate (0.97 mL, 1.58 mmol, 2 equiv) was added dropwise to a stirred suspension of NaH (63 mg, 1.58 mmol, 2 equiv, 60% dispersion in oil) in a 2:1 mixture of anhydrous DMF:THF (6 mL) at 0°C, and the mixture was stirred at rt for 30 min. A solution of **123** (130 mg, 0.79 mmol, 1 equiv) in dry THF (2 mL) was then added, and the resulting mixture was stirred at 80°C for 6 h. After cooling to rt, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (DCM) to afford lactone **124** in 62% yield.



124

R_f: 0.36 (hexane/EtOAc, 9:1). IR (ATR): 1777 (C=O); 1729 (C=O); 1147 (C-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): Mixture of diastereoisomers A:B (3:2): δ 1.48 (s, 9H, $3CH_3$ $_B$); 1.49 (s, 9H, $3CH_3$ $_A$); 2.36 (ABX system, J = 13.0, 9.7, 4.7, 2H, CH_2CHCO_2tBu $_B$); 2.42-2.49 (m, 1H, ½CH_2CHCO_2tBu $_A$); 2.60-2.70 (m, 1H, ½CH_2CHCO_2tBu $_A$); 3.47-3.71 (m, 3H, $CHCO_2tBu$, OCH_2CH); 4.50-4.65 (m, 3H, $PhCH_2$, OCH_2CH $_B$); 4.71-4.78 (m, 1H, OCH_2CH $_A$); 7.26-7.38 (m, 5H, $5CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): Mixture of diastereoisomers A:B (3:2): δ 28.0 ($3CH_3$); 28.3 (CH_2CHCO_2tBu $_B$); 28.5 (CH_2CHCO_2tBu $_A$); 47.6 ($CHCO_2tBu$ $_B$); 47.8 ($CHCO_2tBu$ $_A$); 71.2 ($PhCH_2$); 73.6 (OCH_2CH $_B$); 73.7 (OCH_2CH $_A$); 77.7 (OCH_2CH $_B$); 77.8 (OCH_2CH $_A$); 82.8 (C_A); 82.9 (C_B); 127.7 ($2CH_{Ar}$ $_A$); 127.8 ($2CH_{Ar}$ $_B$); 127.9 (CH_{Ar} $_B$); 128.0 (CH_{Ar} $_A$); 128.6 ($2CH_{Ar}$ $_B$); 128.62 ($2CH_{Ar}$ $_A$); 137.6 (C_{Ar} $_A$); 137.7 (C_{Ar} $_B$); 166.8 (CO_2tBu $_B$); 167.3 (CO_2tBu $_A$); 171.9 ($CO_{lactone}$ $_B$); 172.6 ($CO_{lactone}$ $_A$).

***tert*-Butyl (5*S*)-5-[(benzyloxy)methyl]-3-fluoro-2-oxotetrahydrofuran-3-carboxylate, 125.** Following the general procedure 7, compound **125** was obtained from lactone **124** (1.70 g, 5.54 mmol) in 99% yield, and it was used in the next step without further purification.

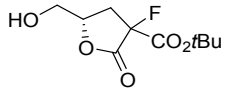


125

R_f: 0.80 (DCM). IR (ATR): 1794 (C=O); 1756 (C=O); 1157 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): Mixture of diastereoisomers A:B (2.3:1): δ 1.48 (s, 9H, $3CH_3$ $_B$); 1.50 (s, 9H, $3CH_3$ $_A$); 2.48-2.81 (m, 2H, CH_2CF); 3.60-3.76 (m, 2H, OCH_2CH); 4.59 (s, 2H, $PhCH_2$);

4.69-4.78 (m, 1H, CH $_A$); 4.81-4.89 (m, 1H, CH $_B$); 7.29-7.38 (m, 5H, 5CH_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): Mixture of diastereoisomers A:B (2.3:1): δ 27.8 (3$CH_{3\ B}$); 27.9 (3$CH_{3\ A}$); 35.1 (d, *J* = 21.9, CH_2CF_B); 35.2 (d, *J* = 22.4, CH_2CF_A); 69.8 (PhCH_2); 73.7 (OCH_2CH_B); 73.8 (OCH_2CH_A); 76.5 (d, *J* = 4.9, CH $_A$); 76.6 (CH $_B$); 85.3 ($C(CH_3)_{3\ B}$); 85.6 ($C(CH_3)_{3\ A}$); 127.7 (2$CH_{Ar\ B}$); 127.8 (2$CH_{Ar\ A}$); 128.0 ($CH_{Ar\ B}$); 128.1 ($CH_{Ar\ A}$); 128.56 (2$CH_{Ar\ B}$); 128.59 (2$CH_{Ar\ A}$); 137.2 ($C_{Ar\ A}$); 137.5 ($C_{Ar\ B}$); 168.5 (d, *J* = 24.8, $CO_{lactone}$); CF and CO_2tBu not observed. MS (ESI, *m/z*): 342.1 $[M+NH_4]^+$.

***tert*-Butyl (5*S*)-3-fluoro-5-(hydroxymethyl)-2-oxotetrahydrofuran-3-carboxylate, 122.** Following the general procedure 3, alcohol **122** was obtained from **125** (480 mg, 1.48 mmol) at 60ºC in quantitative yield.



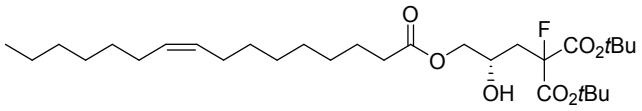
122

R_f: 0.25 (DCM). IR (ATR): 3318 (O-H); 1689 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): Mixture of diastereoisomers A:B (1.2:1): δ 1.52 (s, 9H, 3CH_3); 2.51-2.95 (m, 2H, CH_2CF); 3.66-3.75 (m, 1H, ½CH_2OH); 3.96-4.03 (m, 1H, ½CH_2OH); 4.67-4.75 (m, 1H, CH $_B$); 4.78-4.86 (m, 1H, CH $_A$). ^{13}C-NMR ($CDCl_3$, 75 MHz): Mixture of diastereoisomers A:B (1.2:1): δ 27.9 (3CH_3); 34.2 (d, *J* = 22.4) and 34.3 (d, *J* = 21.9, CH_2CF); 62.5 and 62.8 (CH_2OH); 78.2 (d, *J* = 4.7) and 78.9 (CH); 85.5 and 85.7 ($C(CH_3)_3$); 92.2 (d, *J* = 198.0) and 92.4 (d, *J* = 199.0, CF); 164.5 (d, *J* = 26.9, CO_2tBu); 168.7 (d, *J* = 25.0, $CO_{lactone}$). MS (ESI, *m/z*): 177.9 $[M-t\text{Bu}]^+$; 159.9 $[M-F-t\text{Bu}]^+$.

4.5.2. Synthesis of intermediates 126-131

Di-*tert*-butyl fluoro[(2*S*)-3-{[(9*Z*)-hexadec-9-enoyl]oxy}-2-hydroxypropyl]propanedioate, 126. Following the general procedure 15, ester **126**

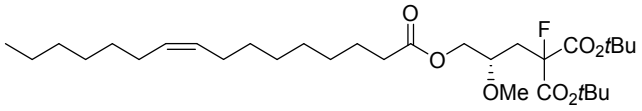
was obtained from palmitoleic acid (106 µL, 0.37 mmol) and alcohol **29** (230 mg, 0.75 mmol) in 44% yield. Chromatography: DCM to DCM/methanol, 8:2.



126

$\underline{R_f}$: 0.61 (hexane/EtOAc, 8:2). $\underline{\text{IR (ATR)}}$: 3401 (O-H); 1744 (C=O); 1150 (C-F). $\underline{^1\text{H-NMR (CDCl}_3\text{, 300 MHz)}}$: δ 0.86 (t, *J* = 6.6, 3H, CH_3); 1.28 (m, 16H, $8CH_2$); 1.48 (s, 18H, $6CH_3$); 1.58-1.63 (m, 2H, $C\underline{H_2}CH_2CO$); 1.96-2.02 (m, 4H, $2C\underline{H_2}CH_{alkene}$); 2.16-2.49 (m, 2H, CH_2CF); 2.32 (t, *J* = 7.5, 2H, CH_2CO); 3.97-4.18 (m, 3H, CH, CO_2CH_2); 5.27-5.38 (m, 2H, $2CH_{alkene}$). $\underline{^{13}\text{C-NMR (CDCl}_3\text{, 75 MHz)}}$: δ 14.2 ($CH_3$); 22.8, 25.0 ($2CH_2$); 27.2, 27.3 ($2\underline{C}H_2CH_{alkene}$); 27.8 ($3CH_3$); 27.9 ($3CH_3$); 29.1, 29.19, 29.2, 29.3, 29.8, 29.83, 31.9 ($7CH_2$); 34.2 ($\underline{C}H_2CO$); 37.5 (d, *J* = 20.7, $\underline{C}H_2CF$); 65.3 (d, *J* = 3.5, CH); 68.0 ($CO_2\underline{C}H_2$); 83.9, 84.0 ($2\underline{C}(CH_3)_3$); 93.1 (d, *J* = 198.2, CF); 129.8, 130.1 ($2CH_{alkene}$); 165.3 (d, *J* = 24.6, $\underline{C}O_2t$Bu); 165.7 (d, *J* = 25.8, $\underline{C}O_2t$Bu); 173.9 (CO). $\underline{[\alpha]_D^{20}}$: +6.7 (c = 1.04, methanol). $\underline{\text{MS (ESI, } m/z\text{)}}$: 562.4 $[M+NH_4]^+$; 567 $[M+Na]^+$.

Di-*tert*-butyl fluoro[(2*S*)-3-{[(9*Z*)-hexadec-9-enoyl]oxy}-2-methoxypropyl]propanedioate, 127. Following the general procedure 10, compound **127** was obtained from **126** (86 mg, 0.16 mmol) in 27% yield. Chromatography: hexane to hexane/EtOAc, 8:2.

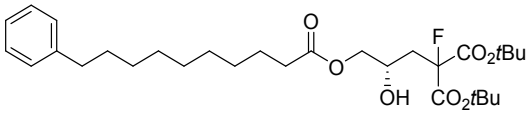


127

$\underline{R_f}$: 0.81 (hexane/EtOAc, 8:2). $\underline{^1\text{H-NMR (CDCl}_3\text{, 300 MHz)}}$: δ 0.88 (t, *J* = 6.7, 3H, CH_3); 1.29 (m, 16H, $8CH_2$); 1.48 (s, 9H, $3CH_3$); 1.49 (s, 9H, $3CH_3$); 1.60-1.64 (m, 2H,

$C\underline{H_2}CH_2CO$); 1.97-2.01 (m, 4H, $2C\underline{H_2}CH_{alkene}$); 2.17-2.50 (m, 2H, CH_2CF); 2.33 (t, *J* = 7.6, 2H, CH_2CO); 3.30 (s, 3H, OCH_3); 3.57-3.64 (m, 1H, CH); 4.05 (dd, *J* = 11.6, 4.9, 1H, $½CO_2CH_2$); 4.17 (dd, *J* = 11.6, 4.7, 1H, $½CO_2CH_2$); 5.28-5.39 (m, 2H, $2CH_{alkene}$). $\underline{^{13}C\text{-NMR (CDCl}_3\text{, 75 MHz)}}$: δ 14.2 ($CH_3$); 22.8, 25.0 ($2CH_2$); 27.3, 27.4 ($2\underline{C}H_2CH_{alkene}$); 27.9 ($3CH_3$); 27.91 ($3CH_3$); 29.1 ($CH_2$); 29.2 ($2CH_2$); 29.3, 29.8, 29.9, 31.9 ($4CH_2$); 34.3 ($\underline{C}H_2CO$); 36.7 (d, *J* = 21.2, $\underline{C}H_2CF$); 57.8 (OCH_3); 64.9 ($CO_2\underline{C}H_2$); 74.0 (d, *J* = 3.4, CH); 83.2, 83.6 ($2\underline{C}(CH_3)_3$); 92.6 (d, *J* = 195.3, CF); 129.9, 130.1 ($2CH_{alkene}$); 165.2 (d, *J* = 27.3, $\underline{C}O_2t$Bu); 165.2 (d, *J* = 24.0, $\underline{C}O_2t$Bu); 173.7 (CO).

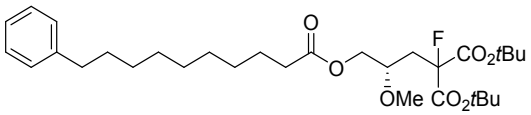
Di-*tert*-butyl fluoro{(2*S*)-2-hydroxy-3-[(10-phenyldecanoyl)oxy]propyl}propanedioate, 128. Following the general procedure 15, ester **128** was obtained from carboxylic acid **53** (65 mg, 0.26 mmol) and alcohol **29** (161 mg, 0.52 mmol) in 75% yield. Chromatography: DCM to DCM/methanol, 99:1.



128

$\underline{R_f}$: 0.43 (hexane/EtOAc, 8:2). $\underline{\text{IR (ATR)}}$: 3387 (O-H); 1743 (C=O); 1154 (C-F). $\underline{^1\text{H-NMR (CDCl}_3\text{, 300 MHz)}}$: δ 1.29 (m, 10H, $5CH_2$); 1.50 (s, 18H, $6CH_3$); 1.56-1.62 (m, 4H, $2CH_2$); 2.17-2.44 (m, 2H, CH_2CF); 2.33 (t, *J* = 7.5, 2H, CH_2CO); 2.59 (t, *J* = 7.8, 2H, $PhC\underline{H_2}$); 4.00-4.20 (m, 3H, CH, CO_2CH_2); 7.17 (d, *J* = 6.5, 3H, $3CH_{Ar}$); 7.24-7.27 (m, 2H, $2CH_{Ar}$). $\underline{^{13}C\text{-NMR (CDCl}_3\text{, 75 MHz)}}$: δ 25.0 ($CH_2$); 27.9 ($3CH_3$); 28.0 ($3CH_3$); 29.2, 29.4, 29.41, 29.5, 29.6, 31.6 ($6CH_2$); 34.3 ($\underline{C}H_2CO$); 36.1 ($Ph\underline{C}H_2$); 37.5 (d, *J* = 20.8, $\underline{C}H_2CF$); 65.4 (d, *J* = 3.5, CH); 68.0 ($CO_2\underline{C}H_2$); 83.9, 84.0 ($2\underline{C}(CH_3)_3$); 93.2 (d, *J* = 196.7, CF); 125.7 (CH_{Ar}); 128.3 ($2CH_{Ar}$); 128.5 ($2CH_{Ar}$); 143.0 (C_{Ar}); 165.2 (d, *J* = 24.6, $\underline{C}O_2t$Bu); 165.6 (d, *J* = 25.9, $\underline{C}O_2t$Bu); 173.9 (CO).

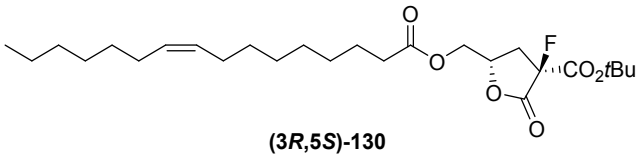
Di-*tert*-butyl fluoro{(2*S*)-2-methoxy-3-[(10-phenyldecanoyl)oxy]propyl} propanedioate, 129. Following the general procedure 10, compound **129** was obtained from **128** (100 mg, 0.19 mmol) in 30% yield. Chromatography: hexane to hexane/EtOAc, 8:2.



129

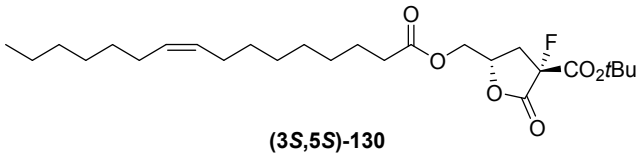
R_f: 0.73 (hexane/EtOAc, 8:2). IR (ATR): 1707 (C=O); 1163 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.25-1.29 (m, 10H, $5CH_2$); 1.48 (s, 9H, $3CH_3$); 1.49 (s, 9H, $3CH_3$); 1.58-1.62 (m, 4H, $2CH_2$); 2.16-2.50 (m, 2H, CH_2CF); 2.32 (t, *J* = 7.5, 2H, CH_2CO); 2.59 (t, *J* = 7.7, 2H, $PhCH_2$); 3.30 (s, 3H, OCH_3); 3.57-3.65 (m, 1H, CH); 4.05 (dd, *J* = 11.7, 4.8, 1H, $½CO_2CH_2$); 4.17 (dd, *J* = 11.7, 4.6, 1H, $½CO_2CH_2$); 7.14-7.19 (m, 3H, $3CH_{Ar}$); 7.24-7.29 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 25.0 (CH_2); 27.9 ($3CH_3$); 27.92 ($3CH_3$); 29.3, 29.4, 29.42, 29.5, 29.6, 31.6 ($6CH_2$); 34.3 (CH_2CO); 36.1 ($PhCH_2$); 36.7 (d, *J* = 21.4, CH_2CF); 57.8 (OCH_3); 64.9 (CO_2CH_2); 74.0 (d, *J* = 3.4, CH); 83.4, 83.6 ($2C(CH_3)_3$); 92.6 (d, *J* = 195.4, CF); 125.7 (CH_{Ar}); 128.4 ($2CH_{Ar}$); 128.5 ($2CH_{Ar}$); 143.0 (C_{Ar}); 165.2 (d, *J* = 27.5 CO_2tBu); 165.24 (d, *J* = 23.9, CO_2tBu); 173.7 (CO). $[\alpha]_D^{20}$: +3.0 (c = 1.69, methanol). MS (MALDI, *m/z*): 570.9 $[M+NH_4]^+$.

***tert*-Butyl (3*R*,5*S*)-3-fluoro-5-{[(9*Z*)-hexadec-9-enoyloxy]methyl}-2-oxotetrahydrofuran-3-carboxylate, (3*R*,5*S*)-130 and *tert*-butyl (3*S*,5*S*)-3-fluoro-5-{[(9*Z*)-hexadec-9-enoyloxy]methyl}-2-oxotetrahydrofuran-3-carboxylate, (3*S*,5*S*)-130.** Following the general procedure 18, **(3*R*,5*S*)-** and **(3*S*,5*S*)-130** were obtained from palmitoleic acid (120 mg, 0.47 mmol) and alcohol **122** (105 mg, 0.45 mmol) in 25% and 21% yield, respectively. Chromatography: hexane to hexane/EtOAc, 4:1.



(3*R*,5*S*)-130

(3*R*,5*S*)-130. R_f: 0.47 (hexane/EtOAc, 4:1). IR (ATR): 1746 (C=O); 1016 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.9, 3H, CH_3); 1.23-1.37 (m, 16H, $8CH_2$); 1.53 (s, 9H, $3CH_3$); 1.59-1.67 (m, 2H, CH_2CH_2CO); 1.99-2.03 (m, 4H, $2CH_2CH_{alkene}$); 2.37 (t, *J* = 7.6, 2H, CH_2CO); 2.44 (ddd, *J* = 22.9, 13.9, 8.5, 1H, ½CH_2CF); 2.86 (dt, *J* = 13.9, 7.0, 1H, ½CH_2CF); 4.21 (dd, *J* = 12.6, 5.1, 1H, ½$COCH_2$); 4.42 (dd, *J* = 12.6, 2.9, 1H, ½CO_2CH_2); 4.79-4.86 (m, 1H, CH); 5.30-5.39 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 22.8, 24.9, 27.3, 27.4 ($4CH_2$); 28.0 ($3CH_3$); 29.1, 29.21, 29.22, 29.3, 29.8, 29.9, 31.9, 34.1 ($8CH_2$); 35.2 (d, *J* = 22.1, CH_2CF); 63.6 (CO_2CH_2); 75.1 (d, *J* = 4.6, 1H, CH); 85.9 ($C(CH_3)_3$); 91.4 (d, *J* = 206.7, CF); 129.9, 130.2 ($2CH_{alkene}$); 164.3 (d, *J* = 28.4, CO_2tBu); 168.1 (d, *J* = 25.1, $CO_{lactone}$); 173.4 (CO). ^{19}F-NMR ($CDCl_3$, 300 MHz): δ -160.4 (dd, *J* = 23.2, 6.7). $[\alpha]_D^{20}$: +4.4 (c = 0.13, methanol). HRMS (ESI, *m/z*): calculated for $C_{26}H_{42}FO_6$ ($[M-H]^-$): 469.2960, found: 469.2939.

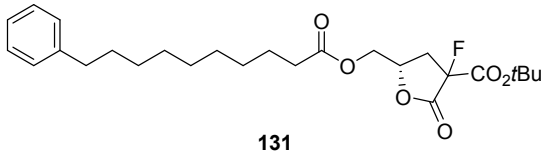


(3*S*,5*S*)-130

(3*S*,5*S*)-130. R_f: 0.53 (hexane/EtOAc, 4:1). IR (ATR): 1745 (C=O); 1119 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, *J* = 6.7, 3H, CH_3); 1.23-1.36 (m, 16H, $8CH_2$); 1.53 (s, 9H, $3CH_3$); 1.57-1.71 (m, 2H, CH_2CH_2CO); 1.97-2.03 (m, 4H, $2CH_2CH_{alkene}$); 2.33-2.38 (m, 2H, CH_2CO); 2.61 (app dd, *J* = 7.5, 4.0, 1H, ½CH_2CF); 2.70 (app dd, *J* = 7.5, 1.1, 1H, ½CH_2CF); 4.24 (dd, *J* = 12.4, 6.2, 1H, ½$COCH_2$); 4.40 (dd, *J* = 12.4, 3.6, 1H,

½CO_2CH_2); 4.91 (ddd, *J* = 15.1, 7.2, 3.5, 1H, CH); 5.26-5.42 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.2 (CH_3); 22.8, 24.9, 27.3, 27.34 ($4CH_2$); 28.0 ($3CH_3$); 29.1 (CH_2); 29.2 ($2CH_2$); 29.3, 29.8, 29.9, 31.9, 34.1 ($5CH_2$); 35.1 (d, *J* = 22.8, $\underline{C}H_2CF$); 63.9 ($CO_2\underline{C}H_2$); 75.7 (CH); 85.7 ($\underline{C}(CH_3)_3$); 91.7 (d, *J* = 199.3, CF); 129.8, 130.2 ($2CH_{alkene}$); 164.4 (d, *J* = 26.7, $\underline{C}O_2t$Bu); 168.1 (d, *J* = 23.7, $CO_{lactone}$); 179.1 (CO). ^{19}F-NMR ($CDCl_3$, 300 MHz): δ -160.6 (dd, *J* = 27.0, 25.4). $[\alpha]_D^{20}$: +62.4 (c = 0.03, methanol). HRMS (ESI, *m/z*): calculated for $C_{26}H_{42}FO_6$ ($[M-H]^-$): 469.3000, found: 469.2939.

***tert*-Butyl (5*S*)-3-fluoro-2-oxo-5-{[(10-phenyldecanoyl)oxy] methyl}tetrahydrofuran -3-carboxylate, 131.** Following the general procedure 18, ester **131** was obtained from carboxylic acid **53** (64 mg, 0.26 mmol) and alcohol **122** (60 mg, 0.26 mmol) in 35% yield. Chromatography: DCM.



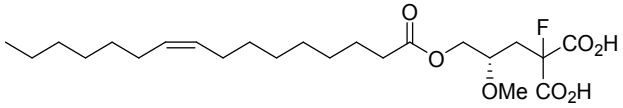
131

R_f: 0.85 (DCM). IR (ATR): 1743 (C=O); 1156 (C-F). ^{1}H-NMR ($CDCl_3$, 300 MHz): Mixture of diastereoisomers A:B (1.7:1): δ 1.28-1.29 (m, 10H, $5CH_2$); 1.53 (s, 9H, $3CH_{3\ B}$); 1.54 (s, 9H, $3CH_{3\ A}$); 1.58-1.63 (m, 4H, $2CH_2$); 2.36 (t, *J* = 7.6, 2H, CH_2CO); 2.41-2.91 (m, 2H, CH_2CF); 2.59 (t, *J* = 7.8, 2H, $PhC\underline{H}_2$); 4.19 (dd, *J* = 10.5, 5.1, 1H, ½$CO_2CH_{2\ B}$); 4.24 (dd, *J* = 11.4, 5.4, 1H, ½$CO_2CH_{2\ A}$); 4.38-4.44 (m, 1H, ½CO_2CH_2); 4.79-4.86 (m, 1H, CH_B); 4.87-4.96 (m, 1H, CH_A); 7.16-7.18 (m, 3H, $3CH_{Ar}$); 7.24-7.30 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): Mixture of diastereoisomers A:B (1.7:1): δ 24.9 (CH_2); 28.0 ($3CH_3$); 29.2, 29.3, 29.4, 29.5, 29.6, 31.6 ($6CH_2$); 34.1 ($\underline{C}H_2CO$); 35.1 (d, *J* = 22.8) and 35.14 (d, *J* = 21.8, $\underline{C}H_2CF$); 36.1 ($Ph\underline{C}H_2$); 63.6 and

63.9 ($CO_2\underline{C}H_2$); 75.1 (d, J = 4.6) and 75.7 (CH); 85.7 and 85.9 ($\underline{C}(CH_3)_3$); 125.7 (CH_{Ar}); 128.4 ($2CH_{Ar}$); 128.5 ($2CH_{Ar}$); 143.02 and 143.04 (C_{Ar}); 164.3 ($\underline{C}O_2t$Bu); 167.8 (d, J = 23.8, $CO_{lactone}$); 173.4 and 173.45 (CO); CF not observed. MS (ESI, *m/z*): 482.3 $[M+NH_4]^+$.

4.5.3. Synthesis of final compounds 69-72

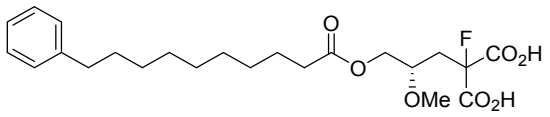
Fluoro[(2*S*)-3-{[(9*Z*)-hexadec-9-enoyl]oxy}-2-methoxypropyl]propanedioic acid, 69. Following the general procedure 1, compound **69** was obtained from *tert*-butyl ester **127** (20 mg, 36 μmol) and TFA (0.21 mL, 2.68 mmol) in 93% yield.



69

^{1}H-NMR (methanol-d_4, 300 MHz): δ 0.90 (t, J = 6.3, 3H, CH_3); 1.29-1.32 (m, 16H, $8CH_2$); 1.57-1.64 (m, 2H, $C\underline{H}_2CH_2CO$); 2.02-2.04 (m, 4H, $2C\underline{H}_2CH_{alkene}$); 2.10-2.59 (m, 2H, CH_2CF); 2.35 (t, J = 7.4, 2H, CH_2CO); 3.32 (s, 3H, OCH_3); 3.60-3.67 (m, 1H, CH); 4.04 (dd, J = 11.8, 4.8, 1H, ½CO_2CH_2); 4.25 (dd, J = 11.7, 4.1, 1H, ½CO_2CH_2); 5.29-5.39 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 14.4 (CH_3); 23.7, 26.0 ($2CH_2$); 28.1, 28.2 ($2\underline{C}H_2CH_{alkene}$); 30.0 ($CH_2$); 30.1 ($2CH_2$); 30.2, 30.8, 30.82, 32.9 ($4CH_2$); 34.9 ($\underline{C}H_2CO$); 38.3 (d, J = 21.3, $\underline{C}H_2CF$); 58.1 (OCH_3); 65.9 ($CO_2\underline{C}H_2$); 75.9 (br s CH); 130.8, 130.9 ($2CH_{alkene}$); 175.2 (CO); $2CO_2H$ and CF not observed. $[\alpha]_D^{20}$: +14.1 (c = 0.79, methanol). HRMS (ESI, *m/z*): calculated for $C_{23}H_{38}FO_7$ ($[M-H]^-$): 445.2607, found: 445.2618. HPLC-MS retention time (min): 11.89.

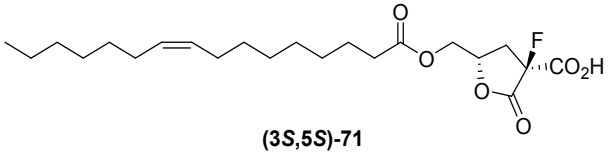
Fluoro{(2*S*)-2-methoxy-3-[(10-phenyldecanoyl)oxy]propyl}propanedioic acid, 70. Following the general procedure 1, compound **70** was obtained from *tert*-butyl ester **129** (44 mg, 80 µmol) and TFA (0.46 mL, 5.97 mmol) in 68% yield.



70

IR (ATR): 3342 (O-H); 1736 (C=O). ^{1}H-NMR (methanol-d_4, 300 MHz): δ 1.28-1.31 (m, 10H, 5CH_2); 1.58-1.62 (m, 4H, 2CH_2); 2.22-2.54 (m, 2H, CH_2CF); 2.34 (t, *J* = 7.4, 2H, CH_2CO); 2.59 (t, *J* = 7.7, 2H, PhCH_2); 3.32 (s, 3H, OCH_3); 3.60-3.65 (m, 1H, CH); 4.04 (dd, *J* = 11.8, 4.8, 1H, ½CO_2CH_2); 4.25 (dd, *J* = 11.7, 4.1, 1H, ½CO_2CH_2); 7.09-7.16 (m, 3H, 3CH_{Ar}); 7.21-7.26 (m, 2H, 2CH_{Ar}). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 26.0, 30.1, 30.2, 30.3 (4CH_2); 30.5 (2CH_2); 32.7 (CH_2); 34.9 (CH_2CO); 36.9 (PhCH_2); 38.1 (d, *J* = 21.3, CH_2CF); 58.1 (OCH_3); 65.8 (CO_2CH_2); 75.8 (d, *J* = 3.4, CH); 126.6 (CH_{Ar}); 129.2 (2CH_{Ar}); 129.4 (2CH_{Ar}); 144.0 (C_{Ar}); 175.2 (CO); 2CO_2H and CF not observed. $[\alpha]_D^{20}$: limited solubility. HRMS (ESI, *m/z*): calculated for $C_{23}H_{32}FO_6$ ([M-H]$^-$): 439.2138, found: 439.2119. HPLC-MS retention time (min): 10.25.

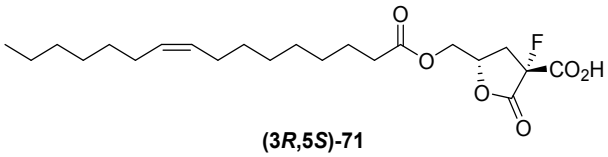
(3*S*,5*S*)-3-Fluoro-5-{[(9*Z*)-hexadec-9-enoyloxy]methyl}-2-oxotetrahydrofuran-3-carboxylic acid, (3*S*,5*S*)-71. Following the general procedure 1, compound **(3*S*,5*S*)-71** was obtained from *tert*-butyl ester **(3*R*,5*S*)-130** (5 mg, 10.5 µmol) and TFA (60.9 µL, 0.79 mmol) in 85% yield.



(3*S*,5*S*)-71

R_f: 0.10 (hexane/EtOAc, 1:1). IR (ATR): 3451 (O-H); 1787 (C=O); 1740 (C=O); 1648 (C=O). ^{1}H-NMR ($CDCl_3$, 700 MHz): δ 0.91 (t, *J* = 6.9, 3H, CH_3); 1.29-1.38 (m, 16H, $8CH_2$); 1.59-1.72 (m, 2H, CH_2CH_2CO); 2.02-2.06 (m, 4H, $2CH_2CH_{alkene}$); 2.39 (t, *J* = 7.5, 2H, CH_2CO); 2.47-2.60 (m, 1H, ½CH_2CF); 2.97-3.09 (m, 1H, ½CH_2CF); 4.26 (dd, *J* = 12.8, 5.1, 1H, ½$COCH_2$); 4.46 (d, *J* = 12.3, 1H, ½CO_2CH_2); 4.92-5.02 (m, 1H, CH); 5.29-5.43 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 175 MHz): δ 14.3 (CH_3); 22.8, 24.9, 27.3, 27.4, 29.2, 29.22, 29.3, 29.8, 31.9, 34.1 ($11CH_2$); 34.9 (CH_2CF); 63.5 (CO_2CH_2); 75.5 (CH); 130.1, 130.4 ($2CH_{alkene}$); 167.9 (br s, CO); 173.7 (CO); CF and CO not observed. $[\alpha]_D^{20}$: +12.4 (c = 0.07, methanol). HRMS (ESI, *m/z*): calculated for $C_{22}H_{34}FO_6$ ($[M-H]^-$): 413.2345, found: 413.2354.

(3*R*,5*S*)-3-Fluoro-5-{[(9*Z*)-hexadec-9-enoyloxy]methyl}-2-oxotetrahydrofuran-3-carboxylic acid, (3*R*,5*S*)-71. Following the general procedure 1, compound **(3*R*,5*S*)-71** was obtained from *tert*-butyl ester **(3*S*,5*S*)-130** (20 mg, 42 μmol) and TFA (250 μL, 3.19 mmol) in 69% yield.

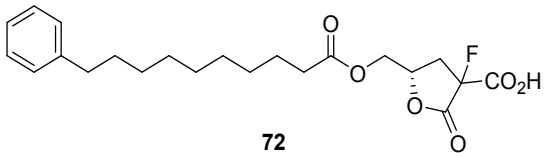


(3*R*,5*S*)-71

R_f: 0.10 (hexane/EtOAc, 1:1). IR (ATR): 3492 (O-H); 1788 (C=O); 1740 (C=O); 1647 (C=O). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.88 (t, *J* = 6.9, 3H, CH_3); 1.15-1.40 (m, 16H, $8CH_2$); 1.57-1.72 (m, 2H, CH_2CH_2CO); 1.92-2.08 (m, 4H, $2CH_2CH_{alkene}$); 2.35-2.39 (m, 2H, CH_2CO); 2.73 (app d, *J* = 7.5, 1H, ½CH_2CF); 2.79 (app dd, *J* = 7.5, 2.1, 1H, ½CH_2CF); 4.28 (dd, *J* = 12.5, 6.0, 1H, ½$COCH_2$); 4.44 (dd, *J* = 12.5, 3.4, 1H, ½CO_2CH_2); 4.94-4.99 (m 1H, CH); 5.28-5.41 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 14.3 (CH_3); 22.8, 24.9, 27.3, 27.4, 29.1, 29.2, 29.22, 29.3, 29.8, 29.9, 31.9

(11CH_2); 34.1 ($\underline{C}H_2CO$); 35.1 (d, J = 22.4, $\underline{C}H_2CF$); 63.7 ($CO_2\underline{C}H_2$); 76.1 (CH); 92.0 (d, J = 199.8, CF); 129.9, 130.2 ($2CH_{alkene}$); 167.3 (d, J = 23.4, CO); 168.6 (d, J = 27.2, CO); 173.6 (CO). $[\alpha]_D^{20}$: +3.0 (c = 0.15, methanol). HRMS (ESI, *m/z*): calculated for $C_{22}H_{34}FO_6$ ([M-H]$^-$): 413.2345, found: 413.2340.

(5*S*)-3-Fluoro-2-oxo-5-{[(10-phenyldecanoyl)oxy]methyl}tetrahydrofuran-3-carboxylic acid, 72. Following the general procedure 1, compound **72** was obtained from *tert*-butyl ester **131** (30 mg, 65 µmol) and TFA (0.37 mL, 4.84 mmol) in 90% yield.



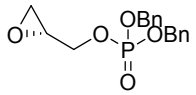
72

IR (ATR): 3506 (O-H); 1795 (C=O); 1795 (C=O); 1741 (C=O). ^{1}H-NMR ($CDCl_3$, 500 MHz): Mixture of diastereoisomers (1:1): δ 1.26-1.30 (m, 10H, 5CH_2); 1.59-1.62 (m, 4H, 2CH_2); 2.36 (t, J = 7.3, 2H, CH_2CO); 2.49-3.06 (m, 2H, CH_2CF); 2.59 (t, J = 7.7, 2H, Ph$\underline{C}H_2$); 4.17-4.30 (m, 1H, ½CO_2CH_2); 4.42-4.49 (m, 1H, ½CO_2CH_2); 4.95-5.03 (m, 1H, CH); 7.16-7.18 (m, 3H, 3CH_{Ar}); 7.25-7.28 (m, 2H, 2CH_{Ar}). ^{13}C-NMR ($CDCl_3$, 125 MHz): Mixture of diastereoisomers (1:1): δ 24.9, 29.2, 29.3, 29.4, 29.5, 29.6, 31.6 (7CH_2); 34.0 and 34.1 ($\underline{C}H_2CO$); 35.1 (br d, J = 25.0, $\underline{C}H_2CF$); 36.1 (Ph$\underline{C}H_2$); 63.5 and 63.9 ($CO_2\underline{C}H_2$); 75.6 (br s) and 76.3 (CH); 125.6 and 125.7 (CH_{Ar}); 128.4 (2CH_{Ar}); 128.5 (2CH_{Ar}); 143.0 and 143.1 (C_{Ar}); 168.0 (br s, CO_2H, $CO_{lactone}$); 173.6 and 173.8 (CO); CF not observed. HRMS (ESI, *m/z*): calculated for $C_{22}H_{28}FO_6$ ([M-H]$^-$): 407.1875, found: 407.1875. HPLC-MS retention time (min): 10.31.

4.6. Synthesis of intermediates (*S*)-, (*R*)-75

4.6.1. Synthesis of bromoalcohols (*S*)-, (*R*)-74

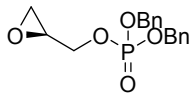
Dibenzyl [(2*R*)-oxiran-2-yl]methyl phosphate, (*R*)-73. Following the general procedure 14, compound **(*R*)-73** was obtained from (2*S*)-oxiran-2-ylmethanol (0.3 mL, 4.52 mmol) and dibenzyl-*N*,*N*-diisopropylphosphoramidite (3.04 mL, 9.04 mmol) in 86% yield. Chromatography: DCM to DCM/EtOAc, 20:1.



(*R*)-73

R_f: 0.35 (hexane/EtOAc, 1:1). IR (ATR): 1275 (P=O); 1013 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.59 (dd, *J* = 4.8, 2.6, 1H, ½$CH_{2\ epox}$); 2.78 (t, *J* = 4.7, 1H, ½$CH_{2\ epox}$); 3.04-3.25 (m, 1H, CH); 3.89 (ddd, *J* = 11.7, 8.5, 5.9, 1H, ½CH_2OP); 4.12-4.27 (m, 1H, ½CH_2OP); 4.97-5.15 (m, 4H, 2PhCH_2); 7.35 (app s, 10H, 10CH_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 44.7 ($CH_{2\ epox}$); 50.0 (d, *J* = 8.0, CH); 68.1 (d, *J* = 5.5, CH_2OP); 69.6 (d, *J* = 5.3, PhCH_2); 69.61 (d, *J* = 5.5, PhCH_2); 128.1 (4CH_{Ar}); 128.7 (6CH_{Ar}); 135.8 (d, *J* = 6.8, 2C_{Ar}). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ 2.03. $[\alpha]_D^{20}$: -8.8 (c = 1.00, methanol). MS (ESI, *m/z*): 335.9 $[M+H]^+$.

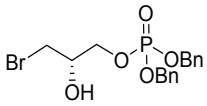
Dibenzyl [(2*S*)-oxiran-2-yl]methyl phosphate, (*S*)-73. Following the general procedure 14, compound **(*S*)-73** was obtained from (2*R*)-oxiran-2-ylmethanol (250 mg, 3.37 mmol) and dibenzyl-*N*,*N*-diisopropylphosphoramidite (2.33 g, 6.75 mmol) in 95% yield. Chromatography: DCM to DCM/EtOAc, 9:1. The spectroscopic data are in agreement with those reported for **(*R*)-73**.



(*S*)-73

$[\alpha]_D^{20}$: +1.2 (c = 1.20, methanol).

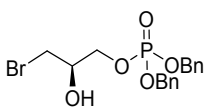
Dibenzyl (2*S*)-3-bromo-2-hydroxypropyl phosphate, (*S*)-74. Following the general procedure 17, bromoalcohol **(*S*)-74** was obtained from oxirane **(*R*)-73** (990 mg, 2.96 mmol) in 89% yield.



(*S*)-74

R_f: 0.41 (DCM/EtOAc, 10:1). IR (ATR): 3371 (O-H); 1009 (P=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.96 (br s, 1H, OH); 3.36 (d, *J* = 5.7, 2H, CH_2Br); 3.88-3.95 (m, 1H, CH); 4.06-4.12 (m, 2H, CH_2OP); 5.00-5.12 (m, 4H, 2PhCH_2); 7.36 (app s, 10H, 10CH_{Ar}). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 33.3 (CH_2Br); 69.2 (d, *J* = 6.0, CH_2OP); 69.7 (d, *J* = 6.6, CH); 70.3 (d, *J* = 5.8, PhCH_2); 70.4 (d, *J* = 5.6, PhCH_2); 128.3 (4CH_{Ar}); 128.9 (4CH_{Ar}); 129.1 (2CH_{Ar}); 135.3 (d, *J* = 6.3, 2C_{Ar}). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ 2.48. $[\alpha]_D^{20}$: -2.1 (c = 1.44, methanol). MS (ESI, *m/z*): 414.8 [M(^{79}Br)+H]$^+$; 416.8 [M(^{81}Br)+H]$^+$.

Dibenzyl (2*R*)-3-bromo-2-hydroxypropyl phosphate, (*R*)-74. Following the general procedure 17, bromoalcohol **(*R*)-74** was obtained from oxirane **(*S*)-73** (1 g, 2.99 mmol) in 99% yield. The spectroscopic data are in agreement with those reported for **(*S*)-73**.

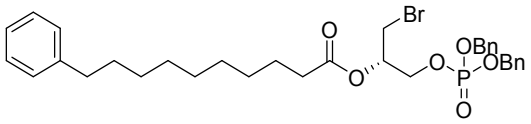


(*R*)-74

$[\alpha]_D^{20}$: +2.2 (c = 0.69, methanol)

4.6.2. Synthesis of intermediates (*S*)-, (*R*)-75

(2*S*)-1-{[Bis(benzyloxy)phosphoryl]oxy}-3-bromopropan-2-yl 10-phenyldecanoate, (*S*)-75. Following the general procedure 18, ester **(*S*)-75** was obtained from carboxylic acid **53** (65 mg, 0.26 mmol) and bromoalcohol **(S)-74** (109 mg, 0.26 mmol) in 68% yield. Chromatography: hexane to hexane/EtOAc, 6:4.

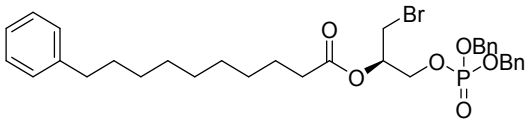


(*S*)-75

R_f: 0.66 (hexane/EtOAc, 7:3). IR (ATR): 1741 (C=O); 1274 (P=O); 1012 (P-O). ^{1}H-NMR (methanol-d_4, δ)(300 MHz): δ 1.22-1.34 (m, 10H, 5CH_2); 1.52-1.63 (m, 4H, 2CH_2); 2.28 (dt, *J* = 7.4, 2.0, 2H, CH_2CO); 2.58 (t, *J* = 7.6, 2H, CH_2Ph); 3.48 (ABX system, *J* = 11.0, 6.0, 5.4, 2H, CH_2Br); 4.17 (m, 2H, CH_2OP); 5.00-5.09 (m, 4H, 2OCH_2Ph); 5.10-5.17 (m, 1H, CH); 7.10-7.16 (m, 3H, 3CH_{Ar}); 7.21-7.26 (m, 2H, 2CH_{Ar}); 7.33-7.39 (m, 10H, 10CH_{Ar}). ^{13}C-NMR (methanol-d_4, δ)(75 MHz): δ 25.9, 30.0, 30.1, 30.25, 30.29, 30.46, 30.49 (7CH_2); 32.7 (CH_2Br); 34.9 (CH_2CO); 36.9 (PhCH_2); 67.9 (d, *J* = 5.5, CH_2OP); 71.0 (d, *J* = 5.9, 2OCH_2Ph); 72.1 (d, *J* = 7.3, CH); 126.6 (CH_{Ar}); 129.2 (6CH_{Ar}); 129.4 (2CH_{Ar}); 129.7 (4CH_{Ar}); 129.8 (2CH_{Ar}); 137.0 (d, *J* = 6.8, 2C_{Ar}); 143.8 (C_{Ar}); 174.1 (CO). ^{31}P-NMR (methanol-d_4, 121 MHz): δ 1.45. $[\alpha]_D^{20}$: +0.6 (c = 0.92, methanol). MS (ESI, *m/z*): 432.0 [M(^{79}Br)-2OCH_2Ph]$^+$; 434.0 [M(^{81}Br)-2OCH_2Ph]$^+$.

(2*R*)-1-{[Bis(benzyloxy)phosphoryl]oxy}-3-bromopropan-2-yl 10-phenyldecanoate, (*R*)-75. Following the general procedure 18, ester **(*R*)-75** was

obtained from carboxylic acid **53** (65 mg, 0.26 mmol) and bromoalcohol **(*R*)-74** (109 mg, 0.26 mmol) in 73% yield. Chromatography: hexane to hexane/EtOAc, 6:4. The spectroscopic data are in agreement with those reported for **(*S*)-75**.



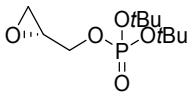
(*R*)-75

$[\alpha]_D^{20}$: -0.1 (c = 1.40, methanol)

4.7. Synthesis of intermediates 80-84

4.7.1. Synthesis of bromoalcohol 80

Di-*tert*-butyl [(2*R*)-oxiran-2-yl]methyl phosphate, 132. Following the general procedure 14, compound **132** was obtained from (2*S*)-oxiran-2-ylmethanol (0.18 mL, 2.69 mmol) and di-*tert*-butyl *N*,*N*-diisopropylphosphoramidite (1.7 mL, 5.39 mmol) in 52% yield. Chromatography: hexane to EtOAc.

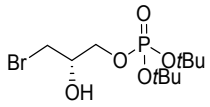


132

R_f: 0.5 (hexane/EtOAc, 1:1). IR (ATR): 1263 (P=O); 999 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.48 (s, 9H, $3CH_3$); 1.49 (s, 9H, $3CH_3$); 2.66 (dd, *J* = 4.7, 2.6, 1H, ½$CH_{2\ epox}$); 2.83 (t, *J* = 4.7, 1H, ½$CH_{2\ epox}$); 3.21-3.27 (m, 1H, CH); 3.85-3.94 (m, 1H, ½CH_2OP); 4.10-4.18 (m, 1H, ½CH_2OP). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.9 ($3CH_3$);

30.0 ($3CH_3$); 44.9 ($CH_{2\ epox}$); 50.3 (d, *J* = 9.0, CH); 67.4 (d, *J* = 5.8, CH_2OP); 82.8 (d, *J* = 7.4, C); 82.83 (d, *J* = 7.4, C). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ -6.90. $[\alpha]_D^{20}$: -9.2 (c = 1.02, methanol). MS (ESI, *m/z*): 289.0 $[M+Na]^+$.

(2*S*)-3-Bromo-2-hydroxypropyl di-*tert*-butyl phosphate, 80. Following the general procedure 17, bromoalcohol **80** was obtained from oxirane **132** (210 mg, 0.79 mmol) in 95% yield.

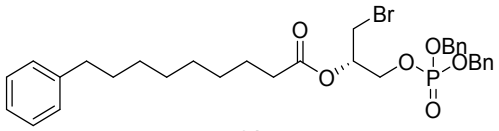


80

R_f: 0.37 (hexane/EtOAc, 1:1). IR (ATR): 3342 (O-H); 1251 (P=O); 996 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.50 (s, 18H, $6CH_3$); 3.49 (d, *J* = 6.0, 2H, CH_2Br); 4.00-4.06 (m, 1H, CH); 4.12-4.17 (m, 2H, CH_2OP); 6.34 (br s, 1H, OH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.9 ($3CH_3$); 30.0 ($3CH_3$); 33.4 (CH_2Br); 68.5 (d, *J* = 6.3, CH_2OP); 70.1 (d, *J* = 6.2, CH); 84.5 (d, *J* = 7.4, C); 84.53 (d, *J* = 7.4, C). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ -7.05. $[\alpha]_D^{20}$: +3.2 (c = 1.11, methanol). MS (ESI, *m/z*): 369.0 $[M(^{79}Br)+Na)]^+$; 371.0 $[M(^{81}Br)+Na)]^+$.

4.7.2. Synthesis of intermediates 81-84

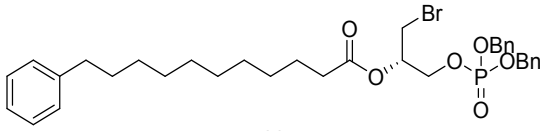
(2*S*)-1-{[Bis(benzyloxy)phosphoryl]oxy}-3-bromopropan-2-yl 9-phenylnonanoate, 81. Following the general procedure 18, ester **81** was obtained from carboxylic acid **52** (122 mg, 0.52 mmol) and bromoalcohol **(*S*)-74** (216 mg, 0.52 mmol) in 96% yield. Chromatography: DCM to DCM/EtOAc, 9:1.



81

R_f: 0.90 (DCM/EtOAc, 10:1). IR (ATR): 1741 (C=O); 1269 (P=O); 1015 (P-O). ^{1}H-NMR (methanol-d_4, 300 MHz): δ 1.27-1.28 (m, 8H, 4CH_2); 1.52-1.63 (m, 4H, 2CH_2); 2.28 (dt, J = 7.5, 1.8, 2H, CH_2CO); 2.57 (t, J = 7.5, 2H, PhCH_2); 3.47 (ABX system, J = 11.1, 6.0, 5.3, 2H, CH_2Br); 4.17 (m, 2H, CH_2OP); 5.04 (d, J = 2.8, 2H, OCH_2Ph); 5.07 (d, J = 2.9, 2H, OCH_2Ph); 5.10-5.17 (m, 1H, CH); 7.10-7.15 (m, 3H, 3CH_{Ar}); 7.21-7.26 (m, 2H, 2CH_{Ar}); 7.31-7.39 (app s, 10H, 10CH_{Ar}). ^{13}C-NMR (methanol-d_4, 75 MHz): δ 24.9, 29.0, 29.1, 29.2, 29.3, 29.4 (6CH_2); 31.7 (CH_2Br); 33.9 (CH_2CO); 35.9 (PhCH_2); 66.9 (d, J = 5.5, CH_2OP); 70.0 (d, J = 5.9, 2OCH_2Ph); 71.1 (d, J = 7.6, CH); 125.6 (CH_{Ar}); 128.2 (4CH_{Ar}); 128.3 (2CH_{Ar}); 128.4 (2CH_{Ar}); 128.8 (4CH_{Ar}); 128.9 (2CH_{Ar}); 135.95, 136.0, 143.0 (3C_{Ar}); 173.1 (CO). ^{31}P-NMR (methanol-d_4, 121 MHz): δ 1.47. $[\alpha]_D^{20}$: +0.6 (c = 0.92, methanol). MS (ESI, *m/z*): 631.2 [M(^{79}Br)+H]$^+$; 633.2 [M(^{81}Br)+H]$^+$.

(2*S*)-1-{[Bis(benzyloxy)phosphoryl]oxy}-3-bromopropan-2-yl 11-phenyl undecanoate, 82. Following the general procedure 18, ester **82** was obtained from 11-phenylundecanoic acid (79 mg, 0.30 mmol) and bromoalcohol **(*S*)-74** (125 mg, 0.30 mmol) in 55% yield. Chromatography: DCM to DCM/EtOAc, 9:1.

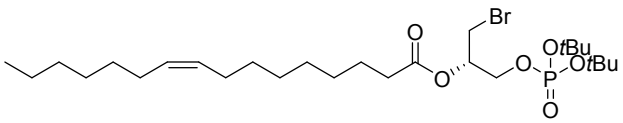


82

R_f: 0.50 (DCM/EtOAc, 10:1). IR (ATR): 1742 (C=O); 1282 (P=O); 1012 (P-O). ^{1}H-NMR (methanol-d_4, δ)(300 MHz): δ 1.26-1.29 (m, 12H, 6CH_2); 1.52-1.63 (m, 4H,

2CH_2); 2.29 (dt, *J* = 7.3, 2.0, 2H, CH_2CO); 2.58 (t, *J* = 7.6, 2H, PhC$\underline{H}_2$); 3.48 (ABX system, *J* = 11.0, 5.9, 5.4, 2H, CH_2Br); 4.17 (m, 2H, CH_2OP); 5.04 (d, *J* = 2.8, 2H, OC$\underline{H}_2$Ph); 5.07 (d, *J* = 2.7, 2H, OC$\underline{H}_2$Ph); 5.13 (qt, *J* = 4.9, 1H, CH); 7.10-7.16 (m, 3H, 3CH_{Ar}); 7.21-7.26 (m, 2H, 2CH_{Ar}); 7.35-7.39 (app s, 10H, 10CH_{Ar}). ^{13}C-NMR (methanol-d_4, δ)(75 MHz): δ 25.9 (CH_2); 30.1 (2CH_2); 30.29, 30.31, 30.5, 30.54, 30.6 (5CH_2); 32.8 (CH_2Br); 34.9 ($\underline{C}H_2CO$); 36.9 (Ph$\underline{C}H_2$); 67.9 (d, *J* = 6.0, CH_2OP); 71.06 (d, *J* = 5.9, O$\underline{C}H_2$Ph); 71.07 (d, *J* = 6.0, O$\underline{C}H_2$Ph); 72.1 (d, *J* = 7.6, CH); 126.6 (CH_{Ar}); 129.2 (6CH_{Ar}); 129.4 (2CH_{Ar}); 129.7 (4CH_{Ar}); 129.9 (2CH_{Ar}); 137.0, 137.1, 144.0 (3C_{Ar}); 174.2 (CO). ^{31}P-NMR (methanol-d_4, 121 MHz): δ 1.44. $[\alpha]_D^{20}$: -2.3 (c = 0.59, methanol). MS (ESI, *m/z*): 659.2 [M(^{79}Br)+H]$^+$; 661.2 [M(^{81}Br)+H]$^+$.

(2*S*)-1-Bromo-3-[(di-*tert*-butoxyphosphoryl)oxy]propan-2-yl (9*Z*)-hexadec-9-enoate, 83. Following the general procedure 18, ester **83** was obtained from palmitoleic acid (0.25 mL, 0.85 mmol) and alcohol **80** (300 mg, 0.85 mmol) in 55% yield. Chromatography: hexane to hexane/EtOAc, 6:1.

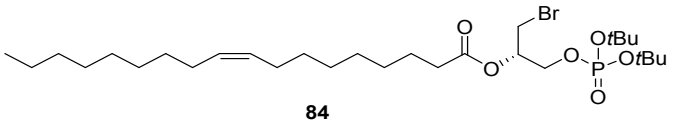


83

R_f: 0.38 (hexane/EtOAc, 8:2). IR (ATR): 1703 (C=O); 1003 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.81 (t, *J* = 6.7, 3H, CH_3); 1.17-1.28 (m, 16H, 8CH_2); 1.42 (s, 18H, 6CH_3); 1.52-1.61 (m, 2H, C$\underline{H}_2CH_2CO$); 1.90-1.96 (m, 4H, 2C$\underline{H}_2CH_{alkene}$); 2.28 (t, *J* = 7.5, 2H, CH_2CO); 3.45 (dd, *J* = 10.9, 5.2, 1H, ½CH_2Br); 3.54 (dd, *J* = 10.9, 5.5, 1H, ½CH_2Br); 4.02-4.09 (m, 2H, CH_2OP); 5.08 (qt, *J* = 5.2, 1H, CH); 5.22-5.33 (m, 2H, 2CH_{alkene}). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 22.8, 25.0 (2CH_2); 27.3, 27.37 (2$\underline{C}H_2CH_{alkene}$); 29.1, 29.21, 29.23, 29.3, 29.7, 29.8, 29.9 (7CH_2); 29.94 (C($\underline{C}H_3$)$_3$); 30.0

($C(\underline{C}H_3)_3$); 31.9 (CH_2Br); 34.9 ($\underline{C}H_2CO$); 65.1 (d, J = 5.9, CH_2OP); 70.7 (d, J = 9.2, CH); 83.0 (d, J = 7.2, C); 83.1 (d, J = 7.6, C); 129.9, 130.2 ($2CH_{alkene}$); 172.9 (CO). HRMS (ESI, *m/z*): calculated for $C_{27}H_{52}Na^{79}BrO_6P$ ($[M(^{79}Br)+Na]^+$): 605.2585, found: 605.2602; calculated for $C_{27}H_{52}Na^{81}BrO_6P$ ($[M(^{81}Br)+Na]^+$): 607.2581, found: 607.2582.

(2*S*)-1-Bromo-3-[(di-*tert*-butoxyphosphoryl)oxy]propan-2-yl (9*Z*)-octadec-9-enoate, 84. To a stirred solution of bromoalcohol **80** (80 mg, 0.23 mmol, 1.1 equiv) in 1.5 mL of anhydrous DCM at rt, pyridine (34 µL, 0.42 mmol, 2 equiv) was added, followed by oleoyl chloride (69 µL, 0.21 mmol, 1 equiv). The reaction mixture was stirred overnight at rt. Afterward, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (alumina, hexane to hexane/EtOAc, 10:1) to afford pure ester **84** in 15% yield.



84

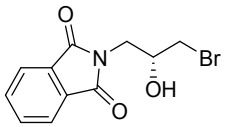
$\underline{R_f}$: 0.64 (DCM/EtOAc, 20:1). IR (ATR): 1744 (C=O); 1002 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, J = 6.5, 3H, CH_3); 1.18-1.39 (m, 20H, $10CH_2$); 1.49 (s, 18H, $6CH_3$); 1.57-1.71 (m, 2H, CH_2); 1.95-2.06 (m, 4H, $2C\underline{H}_2CH_{alkene}$); 2.35 (t, J = 7.7, 2H, CH_2CO); 3.52 (dd, J = 10.9, 5.2, 1H, ½CH_2Br); 3.61 (dd, J = 10.9, 5.4, 1H, ½CH_2Br); 4.05-4.20 (m, 2H, CH_2OP); 5.15 (qt, J = 5.2, 1H, CH); 5.27-5.43 (m, 2H, $2CH_{alkene}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3); 22.8, 25.0 ($2CH_2$); 27.3, 27.4 ($2\underline{C}H_2CH_{alkene}$); 29.2, 29.24, 29.3 ($3CH_2$); 29.5 ($2CH_2$); 29.7, 29.8, 29.9 ($3CH_2$); 29.95 ($3CH_3$); 30.0 ($3CH_3$); 30.1 ($CH_2Br$); 32.1 ($CH_2$); 34.3 ($\underline{C}H_2CO$); 65.1 (d, J = 5.9, CH_2OP); 70.7 (d, J = 9.3, CH); 83.0 (d, J = 7.4, C); 83.05 (d, J = 7.4, C); 129.9, 130.2

($2CH_{alkene}$); 172.9 (CO). ^{31}P-NMR ($CDCl_3$, 121 MHz): δ -7.14. $[\alpha]_D^{20}$: +4.9 (c = 0.66, methanol). MS (ESI, *m/z*): 633.3 $[M(^{79}Br)+Na]^+$; 635.3 $[M(^{81}Br)+Na]^+$.

4.8. Synthesis of intermediates 88-93

4.8.1. Synthesis of amine 88

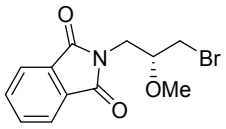
2-[(2*R*)-3-Bromo-2-hydroxypropyl]-1*H*-isoindole-1,3(2*H*)-dione, 133. To a solution of (*R*)-(-)-*N*-(2,3-epoxypropyl)phthalimide (1 g, 4.92 mmol, 1 equiv) in chloroform (6 mL) cooled at 0°C, 48% HBr (7.4 mL) was added dropwise and the reaction was stirred for 30 min. Afterward the mixture was diluted with brine and extracted twice with DCM. The organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure, obtaining **133** without further purification in 96% yield.



133

R_f: 0.73 (hexane/EtOAc, 6:4). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.82 (br s, 1H, OH); 3.52 (ABX system, *J* = 10.7, 5.5, 4.6, 2H, CH_2Br); 3.92 (ABX system, *J* = 14.2, 7.2, 4.3, 2H, NCH_2); 4.09-4.20 (m, 1H, CH); 7.72-7.78 (m, 2H, $2CH_{Ar}$); 7.85-7.91 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 36.6 (CH_2Br); 42.5 (NCH_2); 69.5 (CH); 123.7 ($2CH_{Ar}$); 132.0 ($2C_{Ar}$); 134.4 ($2CH_{Ar}$); 168.8 (2CO). $[\alpha]_D^{20}$: +2.8 (c = 0.28, methanol).

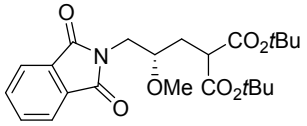
2-[(2*R*)-3-Bromo-2-methoxypropyl]-1*H*-isoindole-1,3(2*H*)-dione, 134. Following the general procedure 10, compound **134** was obtained from **133** (1.32 g, 4.65 mmol) in 62% yield. Chromatography: hexane to hexane/EtOAc, 8:2.



134

R_f: 0.67 (hexane/EtOAc, 6:4). IR (ATR): 1713 (C=O); 1016 (C-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.35-3.51 (m, 2H, CH_2Br); 3.42 (m, 3H, CH_3); 3.65-3.93 (m, 3H, NCH_2, CH); 7.68-7.74 (m, 2H, $2CH_{Ar}$); 7.80-7.86 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 32.3 (CH_2Br); 39.9 (NCH_2); 58.0 (CH_3); 78.0 (CH); 123.5 ($2CH_{Ar}$); 131.9 ($2C_{Ar}$); 134.2 ($2CH_{Ar}$); 168.3 (2CO). $[\alpha]_D^{20}$: +0.96 (c = 0.42, methanol). MS (ESI, *m/z*): 298.0 $[M(^{79}Br)+H]^+$; 300.0 $[M(^{81}Br)+H]^+$.

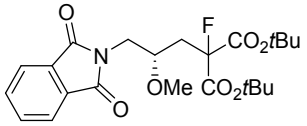
Di-*tert*-butyl [(2*S*)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-methoxypropyl] propanedioate, 135. Di-*tert*-butyl malonate (0.66 mL, 2.94 mmol, 2 equiv) was added dropwise to a stirred suspension of NaH (178 mg, 4.44 mmol, 1.6 equiv, 60% dispersion in oil) in anhydrous DMF (10 mL). Then, **134** (439 mg, 1.47 mmol, 1 equiv) and potassium iodide (269 mg, 1.62 mmol, 1.1 equiv) were added and the mixture was stirred overnight. Then, the solvent was removed under reduced pressure and the residue was dissolved in DCM and washed with 5% aqueous acetic acid, water and brine. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane to hexane/EtOAc, 8:2) to afford **135** in 54% yield.



135

R_f: 0.44 (hexane/EtOAc, 8:2). IR (ATR): 1720 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.44 (s, 18H, $6CH_3$); 1.91-2.11 (m, 2H, CH_2CH); 3.37-3.42 (m, 1H, CH_2CH); 3.38 (m, 3H, OCH_3); 3.51-3.59 (m, 1H, $CHOCH_3$); 3.71-3.85 (m, 2H, NCH_2); 7.68-7.74 (m, 2H, $2CH_{Ar}$); 7.82-7.88 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.0 ($6CH_3$); 31.9 (CH_2CH); 40.4 (NCH_2); 50.6 (CH_2CH); 57.9 (OCH_3); 76.9 ($CHOCH_3$); 81.58, 81.62 ($2C(CH_3)_3$); 123.5 ($2CH_{Ar}$); 132.2 ($2C_{Ar}$); 134.1 ($2CH_{Ar}$); 168.4 (2CON); 168.77, 168.80 (2CO*t*Bu). $[\alpha]_D^{20}$: -1.1 (c = 0.26, methanol). MS (ESI, *m/z*): 456.1 $[M+Na]^+$.

Di-*tert*-butyl [(2*S*)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-methoxypropyl] (fluoro)propanedioate, 136. Following the general procedure 7, compound **136** was obtained from **135** (345 mg, 0.80 mmol) in 96% yield, which was used in the next step without further purification.

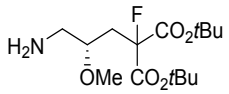


136

R_f: 0.19 (hexane/EtOAc, 9:1). IR (ATR): 1744 (C=O); 1716 (C=O). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.45 (s, 9H, $3CH_3$); 1.47 (s, 9H, $3CH_3$); 2.25-2.45 (m, 2H, CH_2CF); 3.33 (s, 3H, OCH_3); 3.69-3.73 (m, 1H, CH); 3.79-3.80 (m, 2H, NCH_2); 7.71-7.74 (m, 2H, $2CH_{Ar}$); 7.84-7.88 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 27.8 ($3CH_3$); 27.9 ($3CH_3$); 37.8 (*J* = 21.2, CH_2CF); 40.5 (NCH_2); 57.7 (OCH_3); 74.3 (*J* = 3.1, CH); 83.1, 86.6 ($2C(CH_3)_3$); 92.6 (*J* = 195.6, CF); 123.5 ($2CH_{Ar}$); 132.2 ($2C_{Ar}$); 134.2 ($2CH_{Ar}$);

165.16 (J = 25.4, $\underline{C}O_2t$Bu); 165.17 (J = 25.7, $\underline{C}O_2t$Bu); 168.4 (2CON). $[\alpha]_D^{20}$: -1.0 (c = 0.04, methanol). MS (ESI, *m/z*): 469.2 $[M+NH_4]^+$; 474.2 $[M+Na]^+$.

Di-*tert*-butyl [(2*S*)-3-amino-2-methoxypropyl](fluoro)propanedioate, 88. To a solution of phthalimide **136** (378 mg, 0.84 mmol, 1 equiv) in absolute ethanol (8.4 mL), hydrazine monohydrate (1.0 mL, 2.1 mmol 2.5 equiv) was added and the reaction was refluxed for 3 h. Once at rt, the mixture was concentrated under reduced pressure, and the residue was dissolved in DCM and washed with 0.5 N NaOH solution. The aqueous phase was extracted with DCM and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (triethylamine-neutralized silica gel, DCM to DCM/ethanol, 9:1) affording **88** in 66% yield.



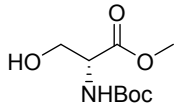
88

R_f: 0.38 (DCM/ethanol, 9:1). IR (ATR): 3353 (N-H); 1746 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.46 (s, 18H, $6CH_3$); 2.08-2.18 (m, 1H, ½CH_2CF); 2.38 (ddd, J = 33.5, 15.2, 8.7, 1H, ½CH_2CF); 2.63-2.68 (m, 1H, ½$NH_2C\underline{H}_2$); 2.87-2.93 (m, 1H, ½$NH_2C\underline{H}_2$); 3.26 (m, 3H, OCH_3); 3.33-3.40 (m, 1H, CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 27.8 ($3CH_3$); 27.9 ($3CH_3$); 36.5 (J = 21.0, $\underline{C}H_2$CF); 44.4 (NH_2CH_2); 57.2 (OCH_3); 77.0 (CH); 83.2, 83.6 ($2\underline{C}(CH_3)_3$); 93.0 (J = 194.9, CF); 165.3 (J = 26.9, $\underline{C}O_2t$Bu); 165.4 (J = 24.4, $\underline{C}O_2t$Bu). MS (ESI, *m/z*): 322.2 $[M+H]^+$.

4.8.2. Synthesis of amine 91

Methyl *N*-(*tert*-butoxycarbonyl)-D-serinate, 137. To a solution of D-serine methyl ester hydrochloride (500 mg, 3.21 mmol, 1 equiv) and triethylamine (0.97 mL, 6.91

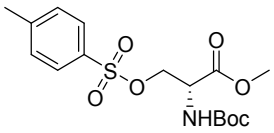
mmol, 2.15 equiv) in anhydrous THF (8 mL), di-*tert*-butyl dicarbonate (700 mg, 3.21 mmol, 1 equiv) was added at 0ºC. The reaction mixture was heated at 140ºC under MW irradiation for 20 min. Once cooled to rt, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc and washed with 1M HCl solution. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure, to afford **137** in 99% yield, which was used in next step without further purification. Spectroscopic data correspond with those previously reported.[7]



137

R_f: 0.23 (hexane/EtOAc, 7:3). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.44 (s, 9H, $3CH_3$); 3.77 (s, 3H, CH_3); 3.91 (qd, J = 11.2, 3.7, 2H, CH_2); 4.31-4.44 (m, 1H, CH); 5.53 (d, J = 7.3, 1H, NH). $[\alpha]_D^{20}$: -0.2 (c = 0.30, methanol).

Methyl *N*-(*tert*-butoxycarbonyl)-*O*-[(4-methylphenyl)sulfonyl]-D-serinate, 138. Following the general procedure 5, tosylate **138** was obtained from **137** (720 mg, 3.28 mmol) in 49% yield. Chromatography: hexane to hexane/EtOAc, 7:3. Spectroscopic data correspond with those previously reported.[8]

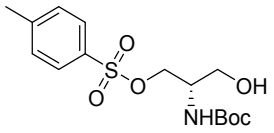


138

R_f: 0.27 (hexane/EtOAc, 8:2). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.41 (s, 9H, $3CH_3$); 2.45 (s, 3H, CH_3C_{Ar}); 3.69 (s, 3H, OCH_3); 4.28 (dd, J = 10.0, 2.9, 1H, ½CH_2); 4.39 (dd,

J = 10.1, 2.8, 1H, ½CH_2); 4.48-4.52 (m, 1H, CH); 5.29 (d, J = 7.6, 1H, NH); 7.35 (d, J = 8.4, 2H, 2CH_{Ar}); 7.76 (d, J = 8.3, 2H, 2CH_{Ar}). $[\alpha]_D^{20}$: -0.3 (c = 0.62, methanol).

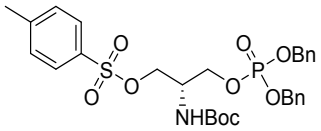
(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxypropyl 4-methylbenzene sulfonate, 139. To a solution of **138** (500 mg, 1.34 mmol, 1 equiv) in absolute ethanol (4 mL) at -5ºC, a suspension of $NaBH_4$ (142 mg, 3.75 mmol, 2.8 equiv) in an ice/water mixture (1 mL) was added. After stirring 1 h at this temperature, the mixture was brought to pH 4 by dropwise addition of glacial acetic acid and ethanol was removed under reduced pressure. Then the residue was dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure, affording **139** in 96% yield.



139

R_f: 0.71 (hexane/EtOAc, 6:4). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.41 (s, 9H, 3CH_3); 2.46 (s, 3H, CH_3C_{Ar}); 3.64 (dd, J = 11.2, 5.1, 1H, ½OCH_2); 3.76-3.90 (m, 2H, ½OCH_2, CH); 4.06-4.18 (m, 2H, CH_2OH); 4.88-4.98 (m, 1H, NH); 7.36 (d, J = 8.0, 2H, 2CH_{Ar}); 7.79 (d, J = 8.3, 2H, 2CH_{Ar}). MS (ESI, *m/z*): 245.9 $[M\text{-}Boc+2H]^+$. HPLC-MS retention time (min): 22.68.

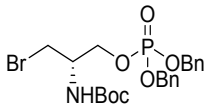
(2*S*)-3-{[Bis(benzyloxy)phosphoryl]oxy}-2-[(*tert*-butoxycarbonyl)amino]propyl 4-methylbenzenesulfonate, 140. Following the general procedure 14, compound **140** was obtained from **139** (150 mg, 0.43 mmol) and dibenzyl-*N*,*N*-diisopropylphosphoramidite (0.29 mL, 0.87 mmol) in 38% yield. Chromatography: hexane to hexane/EtOAc, 6:4.



140

R_f: 0.12 (hexane/EtOAc, 7:3). IR (ATR): 1755 (C=O); 1238 (P=O); 1009 (P-O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.40 (s, 9H, $3CH_3$); 2.41 (s, 3H, CH_3C_{Ar}); 3.81-4.10 (m, 5H, CH_2CHCH_2); 4.86-4.96 (m, 1H, NH); 5.00 (s, 2H, CH_2Ph); 5.03 (s, 2H, CH_2Ph); 7.29-7.39 (m, 12H, $12CH_{Ar}$); 7.73-7.76 (m, 2H, $2CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.8 (CH_3C_{Ar}); 28.4 ($3CH_3$); 49.1 (CH); 65.5 (d, J = 5.9, CH_2OP); 67.4 (OCH_2); 69.81 (d, J = 5.5, CH_2Ph); 69.84 (d, J = 5.6, CH_2Ph); 77.4 ($C(CH_3)_3$); 128.1 ($2CH_{Ar}$); 128.15, 128.2, 128.77, 128.8, 128.9 ($10CH_{Ar}$); 130.1 ($2CH_{Ar}$); 132.5 (C_{Ar}); 135.88 (d, J = 6.3, C_{Ar}); 135.91 (d, J = 6.4, C_{Ar}); 145.3 (C_{Ar}); 155.2 (CO). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 2.02. $[\alpha]_D^{20}$: -0.9 (c = 0.42, methanol). MS (ESI, *m/z*): 513.9 $[M\text{-}CH_2Ph]^+$. HPLC-MS retention time (min): 24.20

***tert*-Butyl (1*S*)-2-{[bis(benzyloxy)phosphoryl]oxy}-1-(bromomethyl)ethyl carbamate, 91.** To a solution of **140** (300 mg, 0.50 mmol, 1 equiv) in acetone (3.5 mL), lithium bromide (86 mg, 0.99 mmol, 2 equiv) was added and the mixture was refluxed for 12 h. Then the solvent was removed under reduced pressure, and the residue was dissolved in EtOAc and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **91** in 79% yield.

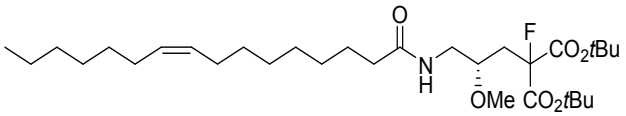


91

R_f: 0.59 (DCM/methanol, 9:1). IR (ATR): 3402 (NH); 1696 (C=O); 1230 (P=O); 1015 (P-O). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.43 (s, 9H, $3CH_3$); 3.34 (dd, *J* = 10.2, 6.6, 1H, ½CH_2Br); 3.44 (dd, *J* = 10.3, 2.8, 1H, ½CH_2Br); 3.98-4.00 (m, 2H, CH, ½CH_2O); 4.17-4.21 (m, 1H, ½CH_2O); 4.98-4.99 (m, 1H, NH); 5.02-5.10 (m, 4H, $2CH_2$Ph); 7.32-7.38 (app s, 10H, $10CH_{Ar}$). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 28.4 ($3CH_3$); 32.0 (CH_2Br); 50.6 (CH); 66.6 (CH_2O); 69.9 ($2CH_2$Ph); 80.4 (C); 128.2 ($4CH_{Ar}$); 128.8 ($4CH_{Ar}$); 128.9 ($2CH_{Ar}$); 135.7 (d, *J* = 6.4, C_{Ar}); 135.71 (d, *J* = 6.1, C_{Ar}); 154.9 (CO). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 2.70. $[\alpha]_D^{20}$: +0.5 (c = 0.46, methanol). MS (ESI, *m/z*): 421.9 [M(^{79}Br)-CH_2Ph]$^-$; 423.9 [M(^{81}Br)-CH_2Ph]$^-$. HPLC-MS retention time (min): 21.92.

4.8.3. Synthesis of intermediates 89, 90, 93

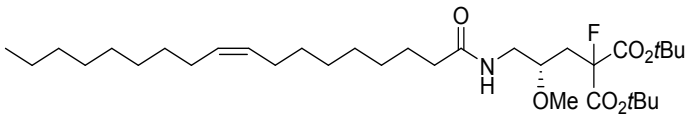
Di-*tert*-butyl fluoro{(2*S*)-3-[(9*Z*)-hexadec-9-enoylamino]-2-methoxypropyl} propanedioate, 89. To a solution of palmitoleic acid (22 µL, 78 µmol, 1 equiv) and **88** (35 mg, 0.11 mmol, 1.4 equiv) in anhydrous DMF (1.95 mL), HOBt (10.5 mg, 78 µmol, 1 equiv) and EDC (17.9 mg, 93 µmol, 1.2 equiv) were added. After stirring for 2 h at rt, additional EDC (6 mg, 0.031 mmol, 0.4 equiv) was added and the reaction was stirred overnight. Then, the mixture was transferred to a separating funnel and a 1:1 mixture of DCM/hexane was added. The solution was washed three times with water, followed by 0.5 N NaOH solution, 0.5 N HCl solution, and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane to hexane/EtOAc, 7:3) affording **89** in 37% yield.



89

R_f: 0.35 (hexane/EtOAc, 8:2). IR (ATR): 3300 (N-H); 1747 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J* = 6.6, 3H, CH_3); 1.25-1.34 (m, 16H, $8CH_2$); 1.45-1.49 (m, 18H, $6CH_3$); 1.58-1.69 (m, 2H, CH_2CH_2CO); 1.97-2.05 (m, 4H, $2CH_2CH_{alkene}$); 2.18 (t, *J* = 7.5, 2H, CH_2CO); 2.10-2.21 (m, 1H, ½CH_2CF); 2.34 (ddd, *J* = 13.7, 6.7, 3.5, 1H, ½CH_2CF); 3.28 (s, 3H, OCH_3); 3.39-3.43 (m, 2H, $NHCH_2$); 3.51-3.58 (m, 1H, CH); 5.28-5.39 (m, 2H, $2CH_{alkene}$); 5.63-5.75 (m, 1H, NH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3); 22.7, 25.8 ($2CH_2$); 27.17, 27.22 ($2CH_2CH_{alkene}$); 27.7 ($3CH_3$); 27.8 ($3CH_3$); 29.0, 29.1, 29.28, 29.3 ($4CH_2$); 29.7 ($2CH_2$); 31.8 (CH_2); 36.77 (d, *J* = 22.1, CH_2CF); 36.8 (CH_2CO); 41.1 (NH_2CH_2); 57.1 (OCH_3); 74.5 (d, *J* = 2.7, CH); 83.1, 83.6 ($2C(CH_3)_3$); 92.7 (*J* = 196.4, CF); 129.8, 130.0 ($2CH_{alkene}$); 165.1 (d, *J* = 23.3, CO_2tBu); 168.8 (d, *J* = 26.3, CO_2tBu); 173.3 (CONH). HRMS (ESI, *m/z*): calculated for $C_{31}H_{56}FNaNO_6$ ([M+Na]$^+$): 580.3984, found: 580.3992.

Di-*tert*-butyl fluoro{(2*S*)-2-methoxy-3-[(9*Z*)-octadec-9-enoylamino]propyl} propanedioate, 90. To a solution of **88** (30 mg, 93 µmol, 1 equiv) in anhydrous DCM (1.4 mL) triethylamine (39 µL, 0.28 mmol, 3 equiv) was added. After stirring at rt for 10 minutes, oleoyl chloride (46 µL, 0.14 mmol, 1.5 equiv) was added and the mixture was stirred for 18 h. Then, water (5 mL) was added and the aqueous layer was extracted with DCM. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane to hexane/EtOAc, 8:2) to afford pure **90** in 46% yield.



90

R_f: 0.29 (hexane/EtOAc, 8:2). IR (ATR): ν 3387 (N-H); 1748 (C=O). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.88 (t, *J* = 6.9, 3H, CH_3); 1.26-1.30 (m, 20H, $10CH_2$); 1.49 (s, 18H, $2C(\underline{C}H_3)_3$); 1.60-1.66 (m, 2H, $\underline{C}H_2CH_2CO$); 1.97-2.04 (m, 4H, $2C\underline{H}_2CH_{alkene}$); 2.13-2.22 (m, 3H, CH_2CO, ½CH_2CF); 2.29-2.40 (m, 1H, ½CH_2CF); 3.29 (s, 3H, OCH_3); 3.36-3.45 (m, 2H, $NHC\underline{H}_2$); 3.53-3.57 (m, 1H, CH); 5.30-5.37 (m, 2H, $2CH_{alkene}$); 5.62-5.67 (br s, 1H, NH). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 14.3 (CH_3); 22.8; 25.9 ($2CH_2$); 27.3; 27.4 ($2\underline{C}H_2CH_{alkene}$); 27.9; 28.0 ($2C(\underline{C}H_3)_3$); 29.3; 29.4; 29.46; 29.47; 29.48; 29.7; 29.89; 29.92; 32.1 ($9CH_2$); 36.9 (d, *J* = 21.3, $\underline{C}H_2CF$); 37.0 ($\underline{C}H_2CO$); 41.3 ($NHCH_2$); 57.3 (OCH_3); 74.6 (d, *J* = 2.7, CH); 83.3; 83.8 ($2\underline{C}(CH_3)_3$); 92.9 (d, *J* = 196.4, CF); 129.9; 130.1 ($2CH_{alkene}$); 166.4 (d, *J* = 24.6, $\underline{C}O_2{}^t$Bu); 166.5 (d, *J* = 26.3, $\underline{C}O_2{}^t$Bu); 173.5 (CONH). $[\alpha]_D^{20}$: -0.68 (c = 0.22, methanol). MS (ESI, *m*/*z*): 586.4 $[M+H]^+$

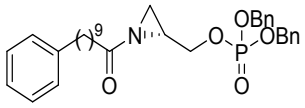
Dibenzyl [(2*R*)-1-(10-phenyldecanoyl)aziridin-2-yl]methyl phosphate, 92.

a) Deprotection of amine **91**: to a solution of **91** (35 mg, 68 μmol, 1 equiv) in anhydrous DCM (0.7 mL), TFA (0.1 mL, 1.36 mmol, 20 equiv) was added and the reaction mixture was stirred at rt overnight. After this time, the solvent was removed by azeotropic distillation with toluene (2x) under reduced pressure to afford the corresponding trifluoroacetate salt in quantitative yield.

b) Activation of carboxylic acid **53**: to a solution of **53** (34 mg, 0.14 mmol, 1 equiv) in anhydrous DCM (2 mL), *N*-hydroxysuccinimide (32 mg, 0.28 mmol, 2 equiv) and EDC (39 mg, 0.21 mmol, 1.5 equiv) were added successively. The reaction was stirred at rt for 12 h. Then the mixture was washed with water, dried over Na_2SO_4, filtered and

concentrated under reduced pressure to afford the corresponding *N*-hydroxysuccinimidyl ester of **53** in quantitative yield, which was used in next step without further purification.

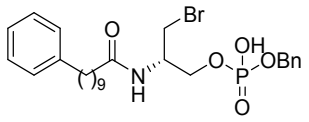
c) Coupling reaction: to a solution of the trifluoroacetate salt of deprotected amine **91** (35 mg, 66 µmol, 1 equiv) in anhydrous DCM (4 mL), triethylamine (46 µL, 0.33 mmol, 5 equiv) and *N*-hydroxysuccinimidyl ester of **53** (45 mg, 0.13 mmol, 2 equiv) were added successively. The reaction was stirred at rt for 12 h. After this time, the mixture was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 3:2 to 1:2) to afford **92** in 48% yield.



92

R_f: 0.55 (EtOAc). IR (ATR): 1702 (C=O); 1261 (P=O); 1018 (P-O). ^{1}H-NMR (methanol-d_4, 700 MHz): δ 1.25-1.32 (m, 10H, $5CH_2$); 1.56-1.61 (m, 4H, $2CH_2$); 2.04 (d, *J* = 2.8, 1H, ½CH_2N); 2.30-2.40 (m, 3H, CH_2CO, ½CH_2N); 2.59 (t, *J* = 7.7, 2H, CH_2Ph); 2.62-2.65 (m, 1H, CH); 3.96 (ddd, *J* = 11.2, 8.6, 6.2, 1H, ½CH_2O); 4.04 (ddd, *J* = 11.8, 7.2, 4.8, 1H, ½CH_2O); 5.02-5.09 (m, 4H, 2OCH_2Ph); 7.16-7.18 (m, 3H, $3CH_{Ar}$); 7.26-7.28 (m, 2H, $2CH_{Ar}$); 7.32-7.37 (m, 10H, $10CH_{Ar}$). ^{13}C-NMR (methanol-d_4, 175 MHz): δ 25.1, 28.4, 29.4, 29.45, 29.50, 29.54, 29.6, 31.7 ($8CH_2$); 34.9 (d, *J* = 8.4, CH); 36.1 (CH_2Ph); 36.6 (CH_2); 68.1 (d, *J* = 5.3, CH_2O); 69.6 (d, *J* = 6.1, OCH_2Ph); 69.7 (d, *J* = 5.4, OCH_2Ph); 125.7, 128.15, 128.17, 128.4, 128.5, 128.78, 128.82 ($15CH_{Ar}$); 135.7, 135.8, 143.1 ($3C_{Ar}$); 185.7 (CO). $[\alpha]_D^{20}$: +6.1 (c = 0.36, methanol). MS (MALDI, *m/z*): 564.3 $[M+H]^+$.

Benzyl (2*S*)-3-bromo-2-[(10-phenyldecanoyl)amino]propyl hydrogen phosphate, 93. To a solution of **92** (4 mg, 7 μmol, 1 equiv) in anhydrous diethyl ether (1 mL), magnesium bromide ethyl etherate (3.7 mg, 14 μmol, 2 equiv) was added and the reaction mixture was stirred at rt for 4 h. After this time, the solvent was removed under reduced pressure to afford compound **93** in quantitative yield.



93

^{1}H-NMR (methanol-d_4, 300 MHz): δ 1.21-1.38 (m, 10H, 5CH_2); 1.53-1.64 (m, 4H, 2CH_2); 2.13-2.25 (m, 2H, CH_2CO); 2.58 (t, J = 7.6, 2H, CH_2Ph); 3.44-3.50 (m, 1H, ½CH_2Br); 3.56-3.63 (m, 1H, ½CH_2Br); 3.84-4.00 (m, 2H, CH_2OP); 4.20-4.33 (m, 1H, CH); 4.85-4.95 (m, 2H, OCH_2Ph); 7.07-7.41 (m, 10H, 10CH_{Ar}). ^{31}P-NMR (methanol-d_4, 121 MHz): δ -0.71. MS (ESI, *m/z*): 552.1 [M(^{79}Br)-H]$^-$; 554.2 [M(^{81}Br)-H]$^-$. HPLC-MS retention time (min): 9.67.

REFERENCES

1. Savariar, E.N.; Aathimanikandan, S.V.; Thayumanavan, S. Supramolecular assemblies from amphiphilic homopolymers: testing the scope. *J. Am. Chem. Soc.* **2006**, *128*, 16224-16230.

2. Iwasaki, T.; Higashikawa, K.; Reddy, V.P.; Ho, W.W.S.; Fujimoto, Y.; Fukase, K.; Terao, J.; Kuniyasu, H.; Kambe, N. Nickel-butadiene catalytic system for the cross-

coupling of bromoalkanoic acids with alkyl grignard reagents: a practical and versatile method for preparing fatty acids. *Chem. Eur. J.* **2013**, *19*, 2956-2960.

3. Cisneros, J. A.; Bjorklund, E.; Gonzalez-Gil, I.; Hu, Y.; Canales, A.; Medrano, F. J.; Romero, A.; Ortega-Gutierrez, S.; Fowler, C. J.; Lopez-Rodriguez, M. L. Structure-activity relationship of a new series of reversible dual monoacylglycerol lipase/fatty acid amide hydrolase inhibitors. *J. Med. Chem.* **2012**, *55*, 824-836.

4. Duffy, P. E.; Quinn, S. M.; Roche, H. M.; Evans, P. Synthesis of *trans*-vaccenic acid and *cis*-9-*trans*-11-conjugated linoleic acid. *Tetrahedron* **2006**, *62*, 4838-4843.

5. Novotný, J.; Pospěchová, K.; Hrabálek, A.; Čáp, R.; Vávrová, K. Synthesis of fluorescent C24-ceramide: evidence for acyl chain length dependent differences in penetration of exogenous NBD-ceramides into human skin. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6975-6977.

6. Jeon, O.Y.; Carreira, E.M. Differential interaction of an AmB analogue and ergosterol in enantiomeric membranes. *Org. Lett.* **2010**, *12*, 1772-1775.

7. Williams, L.; Zhang, Z.; Shao, F.; Carroll, P.J.; Joulli, M.M. Grignard reactions to chiral oxazolidine aldehydes *Tetrahedron* **1996**, *52*, 11673-11694.

8. Boibessot, T.; Bénimèlis, D.; Jean, M.; Benfodda, Z.; Meffre, P. Synthesis of a novel rhizobitoxine-like triazole-containing amino acid. *Synlett* **2016**, *27*, 2685-2688.