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Supporting Information

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Hydride Shift Generated Oxonium Ions: Evidence for Mechanism and Intramolecular Trapping Experiments to Form *Trans* THFs

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Contents

1. Experimental Details

Tetrahydrofuran, dichloromethane, acetonitrile and toluene were purified prior to use by filtration through two activated alumina columns (activated basic aluminium oxide, Brockmann I, standard grade, ~ 150 mesh, 58 Å). Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were used directly.

Flash column chromatography was carried out using silica gel 60 (0.040-0.063 mm) (Merck) using head pressure by means of head bellows. Thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (0.25 mm silica gel with fluorescent indicator UV_{254}). Visualisation was achieved by either the quenching of UV fluorescence or $KMnO_4$, or Vanillin stain.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE AV400 (400 MHz and 100.6 MHz), Bruker DPX400 (400 MHz and 100.6 MHz) or a Bruker AVANCE AV500 (500 MHz and 125.7 MHz) spectrometer. Signal positions were recorded in δ ppm with the abbreviations s, d, t, q, quin., sx, br and m denoting singlet, doublet, triplet, quartet, quintet, sextet, broad and multiplet respectively. All NMR chemical shifts were referenced to residual solvent peaks or to $SiMe_4$ as an internal standard. All coupling constants, *J*, are quoted in Hz.

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Spectra were analysed either as thin films between NaCl plates, KBr disks or in a chloroform solution cell. Mass spectra (*m/z*) and HRMS were recorded under the conditions of electrospray (ESI), chemical (CI) and field (FI) ionisation. Melting points were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

"Petrol" refers to the fraction of petroleum ether boiling in the range 40-60 ºC unless otherwise stated and "ether" refers to diethyl ether.

1.1 General Procedures

General Procedure 1: organic oxidative cyclisation

A solution of diene (1.0 eq) in DCM (100 mL/mmol) was treated with trimethylamine *N*-oxide (4.0 eq) and camphor sulfonic acid (6.0 eq) followed by osmium tetroxide (5 mole %) and stirred for 24 hours. The reaction was monitored by TLC and if any starting material remained was treated with trimethylamine *N*-oxide (4.0 eq) and camphor sulphonic acid (6.0 eq) and stirred for a further 24

hours. This process was repeated until no starting material remained, at which time the reaction was quenched with sodium sulfite (0.1 eq) and sat. Na_2CO_3 solution (100 cm^3/mole), extracted into DCM (3 x 30 mL/mmol), dried (Na_2SO_3) and the solvent removed *in vacuo*.

General Procedure 2: *tert*-butyl silyloxy ethers formation

Di-*tert*-butyl chlorosilane (1.5 eq) was added to a solution of THF (1.0 eq), imidazole (3.0 eq) and DMAP (cat.) in the solvent specified under an atmosphere of Argon and stirred until TLC analysis showed complete consumption of starting material (typically 6-18 hours). The reaction was then diluted with EtOAc (20 mL/mmol) and washed with citric acid (10 mL/mmol), water (10 mL/mmol) and then brine (10 mL/mmol), dried ($MgSO_4$) and the solvent removed *in vacuo*.

General Procedure 3: methanesulfonate ester formation

The substrate (1.0 eq) was dissolved in dichloromethane (10 mL/mmol) and cooled to 0 °C under an atmosphere of Argon. Methanesulfonic anhydride (3.0 eq), and 4-dimethylaminopyridine (4.0 eq) were then added and the mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by addition of a saturated solution of citric acid (10 mL/mmol) and the separated aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*.

General Procedure 4: *intra*-molecular silicon-mediated reduction of THFs

Zinc acetate (5.0 eq) was added to a solution of THF (1.0 eq) in hexafluorispropanol (10 mL/mmol) under an atmosphere of Argon. The solution was stirred at 40 °C for the stated period of time and then cooled to room temperature and diluted with EtOAc (20 mL/mmol). The organic layer was washed with water (10 mL/mmol), brine (10 mL/mmol), dried ($MgSO_4$) and the solvent removed *in vacuo*.

General Procedure 5: TBAF silicon deprotection

TBAF (4.0 eq) was added to a solution of *O*-Silyl THF (1.0 eq) in DMF (1 mL/mmol). The solution was stirred at room temperature for 4 hours. The reaction was then diluted with Et_2O (20 mL/mmol) and water (10 mL/mmol). The organic layer was extracted and the aqueous layer extracted with Et_2O (3 x 10 mL/mmol). The organic layers were then combined and washed with water (3 x 10 mL/mmol) and brine (10 mL/mmol). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*.

General Procedure 6: acidic silyl ether deprotection

Conc. HCl (one drop per mmol) was added to a solution of the substrate (1.0 eq) in methanol (10 mL/mmol). The solution was stirred for 30-60 min, until consumption of starting material. The solvent was removed *in vacuo* and diethyl ether (10 mL/mmol) and water (10 mL/mmol) were added. The separated aqueous layer was extracted with diethyl ether (2 × 10 mL/mmol) and the combined organic layers were washed with brine (20 mL/mmol), dried ($MgSO_4$) and concentrated in vacuo to give a residue which was purified by chromatography as specified.

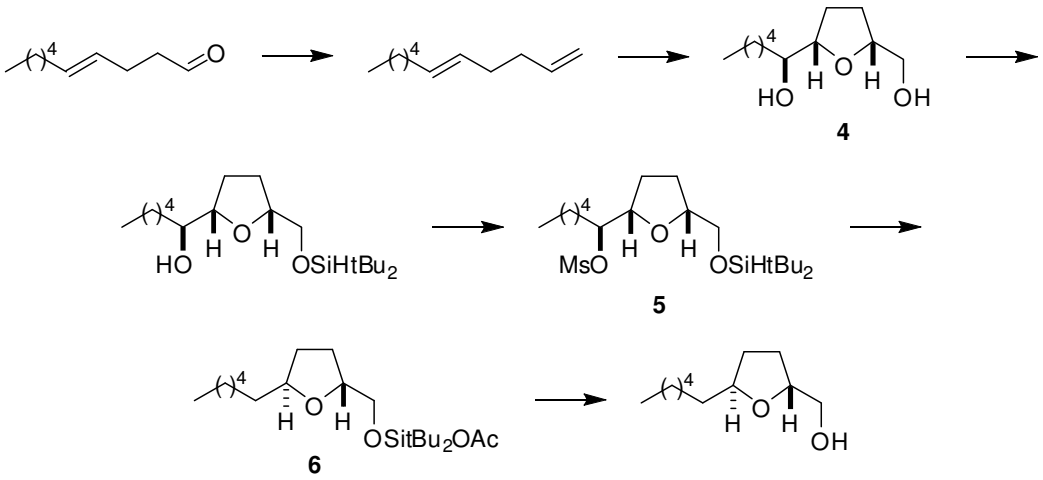
General Procedure 7: *tert*-butyldimethylsilyl ether formation

Imidazole (3.0 eq), *tert*-butyldimethylsilyl chloride (1.5 eq) and 4-dimethylaminopyridine (0.1 eq) were added to a solution of the substrate (1.0 eq) in the solvent specified under an atmosphere of argon. The reaction was stirred for 16 h and then quenched by addition of a saturated solution of citric acid (10 mL/mmol) and stirred for 10 min. The separated aqueous layer was extracted with diethyl ether (3 × 20 mL/mmol) and the combined organic layers were washed with brine (30 mL/mmol), dried ($MgSO_4$) and concentrated in vacuo to give a residue which was purified by chromatography as specified.

General Procedure 8: $AlMe_3$ methyl transfer reaction

The substrate (1.0 eq) was dissolved in dichloromethane (10 mL/mmol) and cooled to 0 °C under an atmosphere of Argon. Trimethylaluminium (2.0 eq, 2M in heptane) was added in one portion followed by dropwise addition of dimethylaluminium chloride (1.0 eq, 1M in heptane). The mixture was stirred for the specified time and then quenched by dropwise addition of either HCl (1M, 5 mL/mmol) or Rochelle's solution (sat., 5 mL/mmol). Diethyl ether (20 mL/mmol) was added and the separated aqueous layer was extracted with diethyl ether (2 × 10 mL/mmol). The combined organic extracts were washed with brine (20 mL/mmol), dried ($MgSO_4$) and concentrated in vacuo to give a residue which was purified by chromatography as specified.

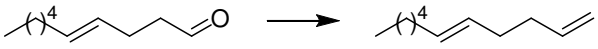
2. Synthesis of THFs 4-6



Scheme 1: Synthesis of THFs 4-6

2.1 Data for starting materials and THFs 4-6

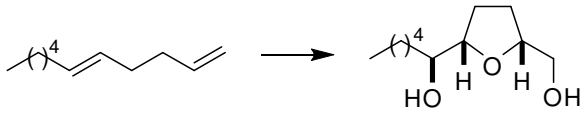
Preparation of (5*E*)-undeca-1,5-diene



BuLi (2.5M in hexanes, 14.5 mL, 36.3 mmol, 1.40 eq) was added to a stirred suspension of methyl triphenylphosphonium bromide (13.9g, 38.9 mmol, 1.50 eq) in THF (100 mL) at 0°C and stirred for 30 minutes. The mixture was then cooled to -78°C and the aldehyde (4.00 g, 26.0 mmol, 1.00 eq) was added dropwise. The reaction mixture was then allowed to warm to room temperature over 16 hours and then quenched with NH_4Cl (20 mL). The mixture was then diluted with Et_2O (200 mL) and washed with water (50 mL) and brine (50 mL), dried and concentrated onto silica. Purification by column chromatography (petrol) yielded the diene (3.85 g, 97%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 2938 (C-H); **δ_H(400 MHz; $CDCl_3$** 5.88-5.77 (1H, m), 5.48-5.37 (2H, m), 5.05-4.94 (2H, m), 2.15-2.06 (4H, m), 2.01-1.95 (2H, m), 1.39-1.22 (8H, m), 0.89 (3H, t, *J* 7.0); **δ_C(100.6 MHz; $CDCl_3$)** 138.6, 131.0, 129.3, 114.4, 33.9, 32.5, 32.0, 31.4, 29.3, 22.5, 14.1 ; **MS (FI, *m/z*)** 152 (M^+, 100%); **HRMS (FI, *m/z*)** $C_{11}H_{20}$ (M^+) requires 152.1565, found 152.1572.

Preparation of (1'*RS*, 2*RS*,5*SR*)-2-(1'-hydroxyhexyl)-5-(hydroxymethyl)tetrahydrofuran 4

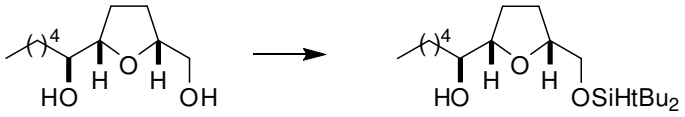


4

Following **General Procedure 1**, a solution of diene (1.0 g, 6.58 mmol) in DCM (500 mL) yielded THF **4** (1.02 g, 77%) as a colourless oil after purification by column chromatography (petrol:acetone 20:1 to 5:1).

IR ν_{max} (film)/cm^{-1} 3385, 2931; **δ_H(400 MHz; $CDCl_3$** 4.11-4.04 (1H, m), 3.85-3.78 (1H, m), 3.76-3.71 (1H, m), 3.52-3.46 (1H, m), 3.45-3.39 (1H, m), 3.16 (2H, s), 1.96-1.67 (4H, m), 1.54-1.22 (8H, m), 0.88 (3H, dt, *J* 2.0, 6.7); **δ_C(100.6 MHz; $CDCl_3$)** 83.2. 80.1, 74.4, 65.1, 34.0, 31.9, 28.2, 27.1, 25.4, 22.6, 14.1; **MS (ESI, *m/z*)** 225 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{11}H_{22}O_3Na$ (M + Na^+) requires 225.1461, found 225.1459.

Preparation of (1'*RS*, 2*RS*, 5*SR*)-2-(1'-hydroxyhexyl)-5-(di-*tert*-butyl silyloxymethyl)tetrahydrofuran

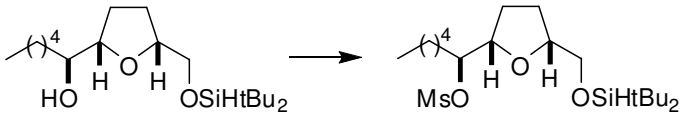


4

Following **General Procedure 2**, THF **4** (750 mg, 3.71 mmol) in DMF (20 mL) yielded the silyl ether (1100 mg, 86%) as a colourless oil after column chromatography (petrol:acetone 100:1 to 40:1).

IR ν_{max} (film)/cm^{-1} 3490, 2931, 2088; **δ_H(400 MHz; $CDCl_3$)** 4.12-4.04 (1H, m), 4.00 (1H, s), 3.87-3.80 (2H, m), 3.73 (1H, ddd, *J* 0.6, 4.2, 10.7), 3.40-3.34 (1H, m), 2.62 (1H, s), 2.00-1.89 (3H, m), 1.83-1.73 (1H, m), 1.56-1.23 (8H, m), 1.02-1.01 (18H, m), 0.89 (3H, t, *J* 6.7); **δ_C(100.6 MHz; $CDCl_3$)** 82.6, 79.9, 75.6, 69.3, 34.3, 31.9, 28.2, 27.5, 27.2, 25.4, 22.6, 20.3, 20.2, 14.1; **MS (ESI, *m/z*)** 367 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{19}H_{40}O_3Si$ (M + Na^+) requires 367.2639, found 367.2639.

Preparation of (1'*RS*, 2*RS*, 5*SR*)- {5- [(di-*tert*-butyl silyloxymethyl)methyl]tetrahydrofuran-2-yl}hexyl methanesulfonate 5

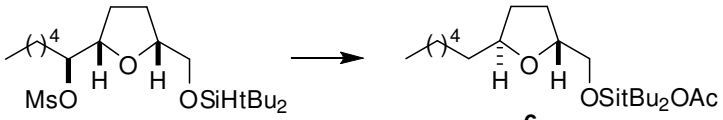


5

Following **General Procedure 3**, the alcohol (400 mg, 1.16 mmol) yielded mesylate **5** (466 mg, 95%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 50:1).

IR ν_{max} (film)/cm^{-1} 2931, 2086; **δ_H(400 MHz; CDCl$_3$)** 4.53 (1H, td, *J* 6.9, 6.1), 4.09-4.03 (1H, m), 3.98 (1H, s) overlapping 4.01-3.95 (1H, m), 3.76 (1H, dd, *J* 5.4, 10.6), 3.68 (1H, dd, *J* 5.2, 10.6), 3.14 (3H, s), 2.04-1.90 (2H, m), 1.85-1.76 (1H, m), 1.66-1.56 (3H, m), 1.54-1.41 (2H, m), 1.36-1.23 (4H, m), 1.00 (18H, s), 0.89 (3H, t, *J* 6.7); **δ_C(100.6 MHz; CDCl$_3$)** 87.0, 80.6, 80.0, 69.5, 38.9, 31.8, 31.5, 27.9, 27.7, 27.2, 24.5, 22.4, 20.2, 20.1, 14.0; **MS (ESI, *m/z*)** 481 (M + MeCN + NH_4^+, 100%), 445 (M + Na^+, 20%); **HRMS (ESI, *m/z*)** $C_{20}H_{42}O_5SiS$ (M + Na^+) requires 445.2414, found 445.2415.

Preparation of (2*RS*, 5*SR*)-2-hexyl-5-{[Acetyl(di-*tert*-Butyl)silyl] oxymethyl}tetrahydrofuran 6

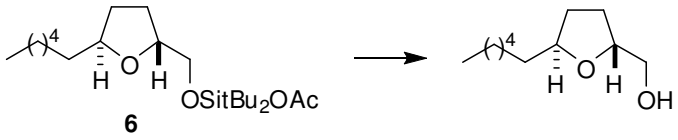


5 **6**

Following **General Procedure 4** THF mesylate **5 (**84 mg, 0.20 mmol) was stirred at 40ºC for 16 hours yielding THF **6** (56 mg, 72%) as a colourless oil after purification by column chromatography (petrol:acetone 300:1 to 100:1).

IR ν_{max} (film)/cm^{-1} 2933, 1735; **δ_H(400 MHz; CDCl$_3$)** 4.06-4.13 (1H, m), 3.98-3.87 (1H, m) overlapping 3.95 (1H, dd, *J* 4.6, 10.2), 3.83 (1H, dd, *J* 5.8, 10.2), 2.11 (3H, s), 2.06-1.95 (2H, m), 1.85-1.75 (1H, m), 1.61-1.20 (11H, m), 1.05 (18H, s), 0.88 (3H, t, *J* 6.7); **δ_C(100.6 MHz; CDCl$_3$)** 169.7, 79.6, 78.5, 67.3, 35.8, 31.9, 31.8, 29.4, 28.2, 27.3, 26.3, 22.8, 22.6, 21.1, 14.1; **MS (ESI, *m/z*)** 445 (M + MeCN + NH_4^+, 100%), 409 (M + Na^+, 30%); **HRMS (ESI, *m/z*)** $C_{21}H_{42}O_4SiNa$ (M + Na^+) requires 409.2745, found 409.2748.

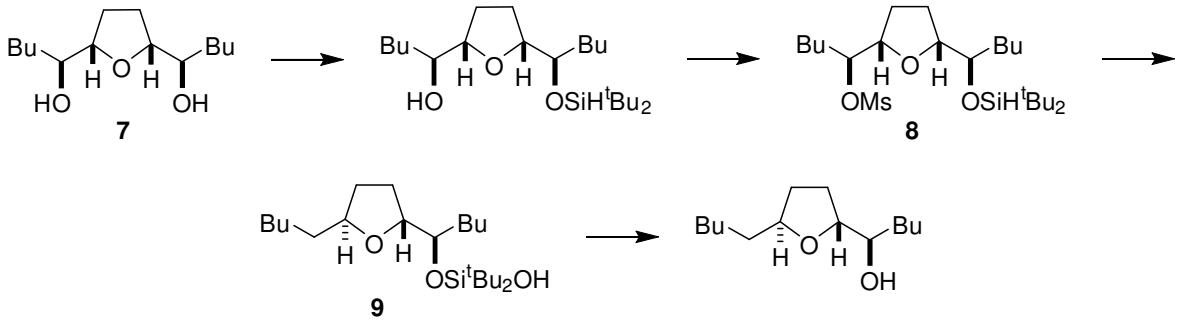
Preparation of (2*RS*, 5*SR*)-2-hexyl-5-(hydroxymethyl)tetrahydrofuran



Following **General Procedure 5** *O*-Silyl THF **6** (16 mg, 0.41 mmol, 1 eq) furnished the alcohol (16 mg, 85%) as a colourless oil after purification by column chromatography (petrol:acetone 100:1 to 50:1). Spectroscopic data were identical to those reported in the literature.[1]

δ_H(400 MHz; $CDCl_3$) 4.11 (1H, dtd, *J* 3.3, 6.5, 7.6), 3.97-3.89 (1H, m), 3.63 (1H, ddd, *J* 3.3, 7.0, 11.3), 3.52-3.46 (1H, m), 2.07-1.92 (3H, m), 1.72-1.23 (11H, m,), 0.89 (3H, t, *J* 6.9); **δ_C(100.6 MHz; $CDCl_3$)** 79.5, 78.8, 65.1, 35.8, 32.1, 31.8, 29.4, 27.5,26.2, 22.6, 14.1.

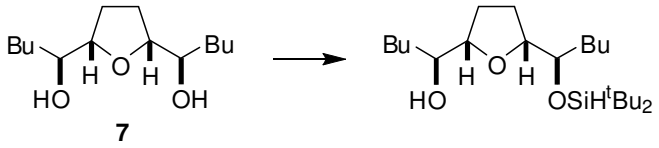
3. Synthesis of THFs 8-9



Scheme 3: Synthesis THFs **8-9**

3.1 Data for starting materials and THFs 8-9

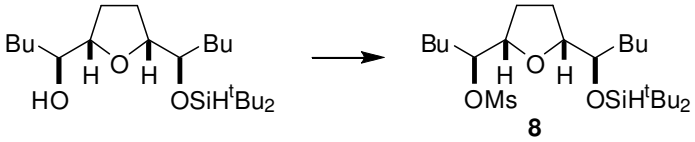
Preparation of (1'*RS*, 1"*SR*, 2*RS*, 5*SR*)-2-(1'-hydroxypentyl)-5-(1"di-*tert*-butyl silyloxypentyl)tetrahydrofuran



Following **General Procedure 2**, alcohol **7** (244 mg, 1.00 mmol) in DCM (10 mL) yielded the silyl ether (260 mg, 67%) as a colourless oil and recovered starting material **7** (44 mg, 18%) after column chromatography (petrol:acetone 100:1 to 5:1).[2]

IR ν_{max} (film)/cm^{-1} 3464, 2932, 2090; **δ_H(400 MHz; CDCl$_3$)** 4.12 (1H, s) , 3.98 (1H, ddd, *J* 4.5, 6.8, 7.9), 3.72 (2H, m), 3.40-3.34 (1H, m), 1.99-1.80 (3H, m), 2.74 (1H, d, *J* 5.6), 1.80-1.61 (3H, m), 1.59-1.25 (10H, m), 1.02-1.00 (18H, m), 0.93-0.87 (6H, m); **δ_C(100.6 MHz; CDCl$_3$)** 82.1, 81.4, 77.0, 74.7, 33.8, 33.3, 28.4, 27.9, 27.5, 23.0, 22.8, 20.5, 20.0, 14.1; **MS (ESI, *m/z*)** 445 (M + MeCN + NH_4^+, 100%), 409 (M + Na^+, 10%); **HRMS (ESI, *m/z*)** $C_{22}H_{46}O_3Si$ (M + Na^+) requires 409.3108, found 409.3107.

Preparation of (1'*RS*, 1"*SR*, 2*RS*, 5*SR*)-{5-[(1"-di-*tert*-butyl silyloxypentyl) tetrahydrofuran-2-yl]pentyl} methanesulfonate 8

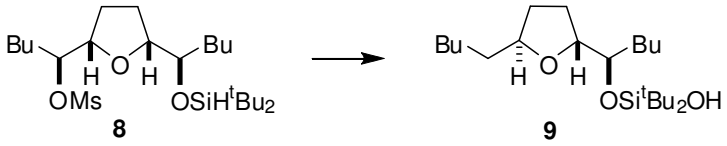


Following **General Procedure 3**, the alcohol (150 mg, 0.388 mmol) yielded THF **8** (160 mg, 89%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 50:1).

IR ν_{max} (film)/cm^{-1} 2932, 2088; **δ_H(400 MHz; CDCl$_3$)** 4.58 (1H, dt, *J* 4.8, 7.2), 4.11 (1H, s), 4.07-4.02 (1H, m), 3.99-3.93(1H, m), 3.80 (1H, dt, *J* 4.0, 6.2), 3.09 (3H, s), 1.94-1.85 (3H, m), 1.69-1.25 (13H, m), 1.00 (9H, s), 0.99 (9H, s), 0.91 (3H, t, *J* 7.2) overlapping 0.90 (3H, t, *J* 7.1); **δ_C(100.6 MHz; CDCl$_3$)** 86.5, 81.0, 80.2, 76.0, 38.7, 32.3, 31.4, 28.4, 27.7, 27.4, 26.9, 26.7, 22.9, 22.5, 20.5, 20.0,

14.0, 13.9; **MS (ESI, *m/z*)** 523 (M + MeCN + NH_4^+, 100%), 487 (M + Na^+, 10%); **HRMS (ESI, *m/z*)** $C_{23}H_{48}O_5SSi$ (M + Na^+) requires 482.3330, found 482.3318.

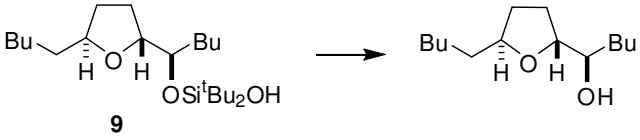
Preparation of (1"*SR*, 2*RS*, 5*SR*)-2-(pentyl)-5-(1"di-*tert*-butyl hydroxysilyloxypentyl)tetrahydrofuran 9



Following **General Procedure 4** mesylate **8** (64 mg, 0.14 mmol) was stirred at 40ºC for 16 hours yielding *trans*-THF **9** (48 mg, 87%) as a colourless oil after purification by column chromatography (petrol:acetone 300:1 to 100:1).

IR ν_{max} (film)/cm^{-1} 3425, 2933; **δ_H(400 MHz; $CDCl_3$)** 4.85 (1H, s), 4.00-3.93 (1H, m), 3.83-3.75 (2H, m), 2.07-2.00 (1H, m), 1.96-1.89 (1H, m), 1.66-1.24 (16H, m), 1.03 (9H, s), 1.00 (9H, s), 0.92-0.83 (6H, m); **δ_C(100.6 MHz; $CDCl_3$)** 83.5, 76.7, 79.5, 33.7, 32.9, 31.9, 29.4, 27.7, 27.4, 26.9, 25.7, 23.0, 22.5, 21.2, 20.3, 14.0; **MS (ESI, *m/z*)** 385 (M - H^+, 100%); **HRMS (ESI, *m/z*)** $C_{22}H_{46}O_3SiNa$ (M + Na^+) requires 409.3108, found 409.3105.

Preparation of (1"*SR*, 2*RS*, 5*SR*)-2-(pentyl)-5-(1"-hydroxypentyl)tetrahydrofuran

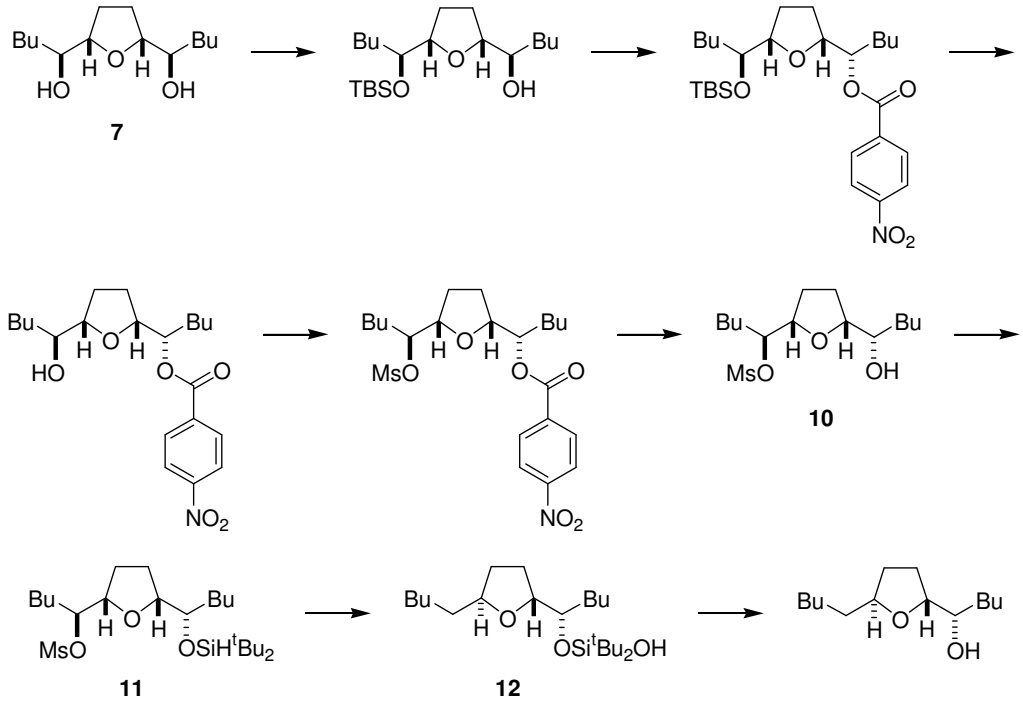


Following **General Procedure 5**, *O*-Silyl THF **9** (37 mg, 0.096 mmol) furnished the THF (20 mg, 91%) as a colourless oil after purification by column chromatography (petrol:acetone 200:1 to 100:1).

IR ν_{max} (film)/cm^{-1} 3454, 2931; **δ_H(400 MHz; $CDCl_3$)** 3.92-3.85 (1H, m), 3.82-3.76 (1H, m), 3.40-3.35 (1H, m), 2.44 (1H, d, *J* 3.1), 2.07-1.93 (2H, m), 1.66-1.25 (16H, m), 0.93-0.86 (6H, m); **δ_C(100.6 MHz; $CDCl_3$)** 81.9, 79.3, 74.2, 35.6, 33.0, 32.4, 31.9, 28.4, 27.8, 25.9, 22.8, 22.6, 14.0; **MS (ESI,**

***m/z*)** 287 (M + MeCN + NH_4^+, 100%), 251 (M + Na^+, 40%); **HRMS (ESI, *m/z*)** $C_{14}H_{28}O_2Na$ (M + Na^+) requires 251.1982, found 251.1981.

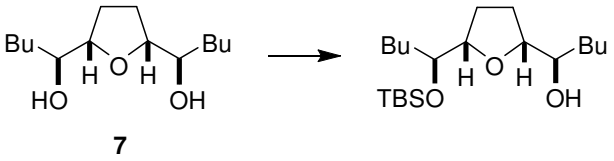
4. Synthesis of THFs 10-12



Scheme 3: Synthesis of THFs **10-12**

4.1 Data for starting materials and THFs 10-12

(R*)-1-((2R*,5S*)-5-((S*)-1-(tert-butyldimethylsilyloxy)pentyl)tetrahydrofuran-2-yl) pentan-1-ol

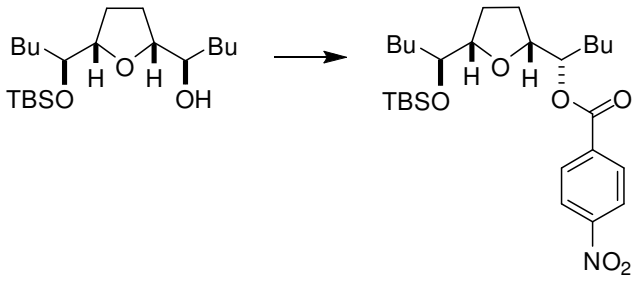


Sodium hydride (60% in oil, 260 mg, 6.49 mmol, 1.10 eq) was added portionwise over 5 min to a solution of the diol **7** (1.44 g, 5.90 mmol, 1.00 eq) in THF (60 mL) at 0 °C under an atmosphere of argon.[2] The suspension was stirred for 10 minutes and then *tert*-butyldimethylsilylchloride (1.16 g,

7.67 mmol, 1.30 eq) was added as a solution in THF (5 mL) and the mixture was stirred for 2 hours and then allowed to warm to room temperature over 16 hours. NH_4Cl (10 mL) was added and the mixture was diluted with diethyl ether (100 mL). The separated aqueous layer was extracted with diethyl ether (2 × 40 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a residue which was purified by by column chromatography (petrol:acetone 200:1 to 50:1) to give the silyl ether (704 mg, 56%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 3474, 2956; **δ_H(400 MHz; $CDCl_3$)** 3.95-3.91 (1H, m), 3.82-3.77 (1H, m), 3.61-3.57 (1H, m), 3.39-3.35 (1H, m), 2.68 (1H, d, *J* 5.4), 1.94-1.75 (4H, m), 1.65-1.60 (2H, m), 1.51-1.28 (10H, m), 0.93-0.89 (15H, m), 0.09 (3H, s), 0.08 (3H, s); **δ_C(100.6 MHz; $CDCl_3$)** 82.1, 81.5, 74.6, 74.2, 34.0, 33.7, 28.2, 28.0, 27.6, 27.5, 25.9, 22.9, 22.8, 18.2, 14.1, 14.0, -4.3, -4.5; **MS (ESI, *m/z*)** 381 (100%, M+Na$^+$); **HRMS (ESI, *m/z*)** $C_{20}H_{43}O_3SiNa$ (M+Na$^+$) require 359.2976, found 359.2972.

Preparation of (1'*SR*, 1"*SR*, 2*RS*, 5*SR*)-(5-{[1" *tert*-butyl(dimethyl) silyloxypentyl] tetrahydrofuran-2-yl}pentyl) 4-nitrobenzoate

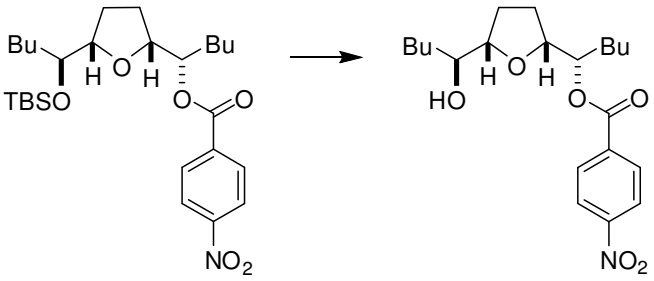


Diisopropylazodicarboxylate (2.31 g, 11.4 mmol, 3.00 eq) was added dropwise over 5 min to a solution of the alcohol (1.36 g, 3.79 mmol, 1.00 eq), triphenylphosphine (3.04 g, 11.4 mmol, 3.00 eq) and 4-nitrobenzoic acid (1.90 g, 11.4 mmol, 3.00 eq) in tetrahydrofuran (40 mL) at 0 °C under an atmosphere of argon. The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was then concentrated onto silica *in vacuo* and yielded the benzoate (1.15 g, 61%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 50:1).

IR ν_{max} (film)/cm^{-1} 2956, 1726; **δ_H(400 MHz; $CDCl_3$)** 8.30 (2H, d, *J* 8.7), 8.22 (2H, d, *J* 8.7), 5.26 (1H, dt, *J* 5.1, 7.3), 4.07-4.01 (1H, m, *J* 6.3), 3.83 (1H, dt, *J* 5.1, 7.3), 3.60-3.58 (1H, m), 1.97-1.91

(1H, m), 1.86-1.72 (4H, m), 1.69-1.63 (1H, m), 1.42-1.09 (10H, m), 0.92-0.87 (12H, m), 0.81 (3H, t, *J* 7.2), 0.06 (3H, s), 0.02 (3H, s); **δ_C(100.6 MHz; $CDCl_3$)** 164.2, 150.5, 136.0, 130.7, 123.5, 82.7, 79.7, 76.7, 74.2, 32.4, 30.7, 27.5, 27.0 , 26.4, 25.9, 22.7, 22.6, 18.2, 14.0, 13.9, -4.2, -4.8; **MS (ESI, *m/z*)** 530 (100%, M + Na^+); **HRMS (ESI, *m/z*)** $C_{27}H_{45}NO_6SiNa$ (M + Na^+) requires 530.2908, found 530.2909.

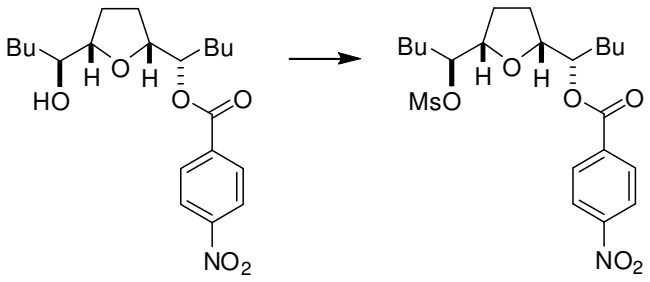
Preparation of (1'*SR*, 1"*SR*, 2*RS*, 5*SR*)-(5-{[1"-(hydroxypentyl)] tetrahydrofuran-2-yl}pentyl) 4-nitrobenzoate



Following **General Procedure 6**, the silyl ether (726 mg, 1.46 mmol) gave the alcohol (503 mg, 87%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 20:1).

IR ν_{max} (film)/cm^{-1} 3551, 2957, 1724; **δ_H(400 MHz; $CDCl_3$)** 8.32-8.29 (2H, m), 8.23-19 (2H, m), 5.37-5.32 (1H, m), 4.16-4.10 (1H, m), 3.78-3.72 (1H, m), 3.26-3.20 (1H, m), 2.15 (1H, br s), 2.05-1.87 (3H, m), 1.76-1.61 (5H, m), 1.43-1.15 (8H, m), 0.92-0.82 (6H, m); **δ_C(100.6 MHz; $CDCl_3$)** 164.5, 150.5, 135.7, 130.7, 123.6, 82.9, 80.4, 76.3, 73.9, 33.3, 30.9, 27.7, 27.6, 27.5, 22.6, 22.5, 14.0, 13.9; **MS (ESI, *m/z*)** 494 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{21}H_{35}N_2O_6$ (M + NH_4^+) requires 411.2490, found 411.2479.

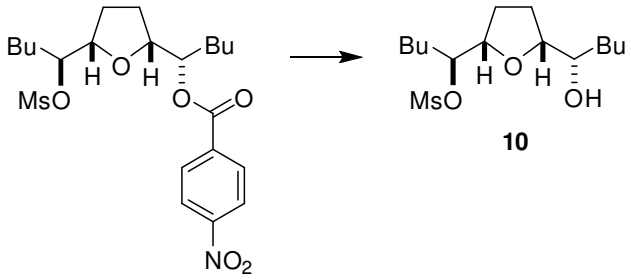
Preparation of (1'*SR*, 1"*SR*, 2*RS*, 5*SR*)-(5-{[1" (methylsulfonyloxy)pentyl)] tetrahydrofuran-2-yl}pentyl) 4-nitrobenzoate



Following **General Procedure 3**, alcohol (683 mg, 1.74 mmol) yielded the mesylate (722 mg, 88%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 20:1).

IR ν_{max} (film)/cm^{-1} 2958, 1724; **δ_H(400 MHz; $CDCl_3$)** 8.32-8.29 (2H, m), 8.23-19 (2H, m), 5.35 (1H, dt, *J* 4.6, 6.5), 4.41-4.36 (1H, m), 4.15-4.10 (1H, m), 4.01-3.95 (1H, m), 3.05 (3H, s), 2.05-1.93 (3H, m), 1.75-1.51 (5H, m), 1.43-1.15 (8H, m), 0.91-0.83 (6H, m); **δ_C(100.6 MHz; $CDCl_3$)** 164.3, 150.3, 135.7, 130.7, 123.5, 85.9, 80.4, 80.3, 75.7, 38.7, 31.3, 30.7, 28.0, 27.5, 26.9, 26.3, 22.5, 22.3, 13.9, 13.8; **MS (ESI, *m/z*)** 494 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{22}H_{33}NO_8SNa$ (M + Na^+) requires 494.1819, found 494.1814.

Preparation of (1'*RS*, 1"*SR*, 2*RS*, 5*SR*)-{5-[(1"-hydroxypentyl)tetrahydrofuran-2-yl]pentyl} methanesulfonate 10



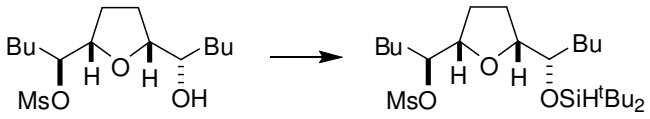
10

K_2CO_3 (632 mg, 4.58 mmol, 3.00 eq) was added to a solution of the benzoate (720 mg, 1.53 mmol, 1.00 eq) in methanol (15 mL) and stirred for 4 hours. The reaction was then diluted with ethyl acetate (100 mL) and washed with water (30 mL) and brine (30 mL), dried and concentrated onto silica.

Purification by column chromatography (petrol:acetone 100:1 to 30:1) yielded the mesylate **10** (420 mg, 86%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 3528, 2957; **δ_H(400 MHz; $CDCl_3$)** 4.63-4.56 (1H, m), 4.01 (1H, dt, *J* 5.6, 7.6), 3.92 (1H, ddd, *J* 2.8, 6.4, 8.0), 3.85-3.80 (1H, m), 3.13 (3H, s), 2.76 (1H, s), 2.09-1.91 (2H, m), 1.83-1.69 (1H, m), 1.68-1.59 (2H, m), 1.55-1.25 (10H, m), 0.92 (3H, t, *J* 7.2), 0.91 (3H, t, *J* 7.2); **δ_C(100.6 MHz; $CDCl_3$)** 86.4, 83.6, 79.9, 71.1, 38.9, 32.4, 31.3, 28.5, 28.2, 27.2, 23.5, 22.7, 22.3, 14.0, 13.8; **MS (ESI, *m/z*)** 345 (M Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{15}H_{30}O_5SNa$ (M + Na^+) requires 345.1706, found 345.1695.

Preparation of (1'*RS*, 1"*RS*, 2*RS*, 5*SR*)-{5-[(1"-di-*tert*-butyl silyloxypentyl) tetrahydrofuran-2-yl]pentyl} methanesulfonate 11

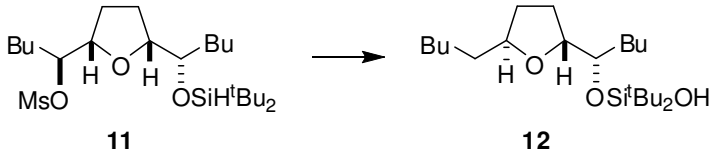


10 **11**

Following **General Procedure 2**, the alcohol **10** (155 mg, 0.481 mmol) in DMF (2.5 mL) yielded silyl ether **11** (204 mg, 91%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 50:1).

IR ν_{max} (film)/cm^{-1} 2932, 2088; **δ_H(400 MHz; $CDCl_3$)** 4.61-4.55 (1H, m), 4.10 (1H, s), 3.92-3.82 (3H, m), 3.10 (3H, s), 1.99-1.84 (3H, m), 1.66-1.24 (13H, m), 1.00 (9H, s), 0.98 (9H, s), 0.90 (3H, t, *J* 7.2) overlapping 0.90 (3H, t, *J* 7.1); **δ_C(100.6 MHz; $CDCl_3$)** 86.5, 81.8, 80.6, 75.8, 38.8, 33.4, 31.6, 28.0, 27.4, 26.8, 26.4, 23.0, 22.4, 20.4, 20.1, 14.0, 13.8; **MS (ESI, *m/z*)** 487 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{23}H_{48}O_5SSiNa$ (M + Na^+) requires 482.3330, found 482.3329.

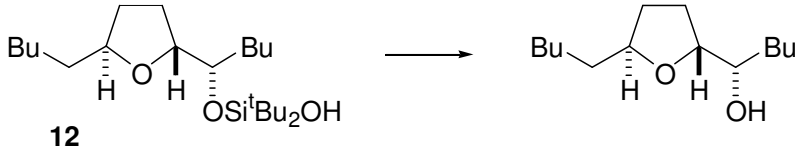
Preparation of (1"*SR*, 2*RS*, 5*SR*)-2-(pentyl)-5-(1"di-*tert*-butyl hydroxysilyloxypentyl)tetrahydrofuran 12



Zinc acetate (62 mg, 0.340mmol, 5.0 eq) was added to a solution of silyl ether **11** (32 mg, 0.069 mmol, 1.0 eq) in hexafluorispropanol (0.07 mL) under an atmosphere of argon. The solution was stirred at 40ºC for 16 hours and then cooled to room temperature. AcOH (2 drops) was then added and the solution was stirred for 1 hour. The mixture was then diluted with EtOAc (20 mL), washed with water (10 mL), brine (10 mL), dried and concentrated onto silica. Purification by column chromatography (petrol:acetone 300:1 to 100:1) yielded the *trans*-THF **12** (23 mg, 87%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 3425, 2933; **δ_H(400 MHz; CDCl$_3$)** 4.46 (1H, br s), 4.29-4.25 (1H, m), 4.10-4.02 (1H, m), 3.86 (1H, ddd, *J* 2.2, 5.2, 10.6), 2.14-2.06 (1H, m), 1.96-1.89 (1H, m), 1.78-1.71 (1H, m), 1.58-1.22 (15H, m), 1.05 (9H, s), 1.00 (9H, s), 0.92-0.86 (6H, m); **δ_C(100.6 MHz; CDCl$_3$)** 81.6, 79.7, 71.4, 36.6, 34.7, 31.9, 31.7, 28.3, 27.8, 25.8, 24.1, 23.0, 22.5, 21.4, 20.5, 14.1, 14.0; **MS (ESI, *m/z*)** 387 (M + H$^+$, 100%); **HRMS (ESI, *m/z*)** $C_{22}H_{46}O_3SiNa$ (M + Na$^+$) requires 409.3108, found 409.3103.

Preparation of (1"*RS*, 2*RS*, 5*SR*)-2-(pentyl)-5-(1"-hydroxypentyl)tetrahydrofuran

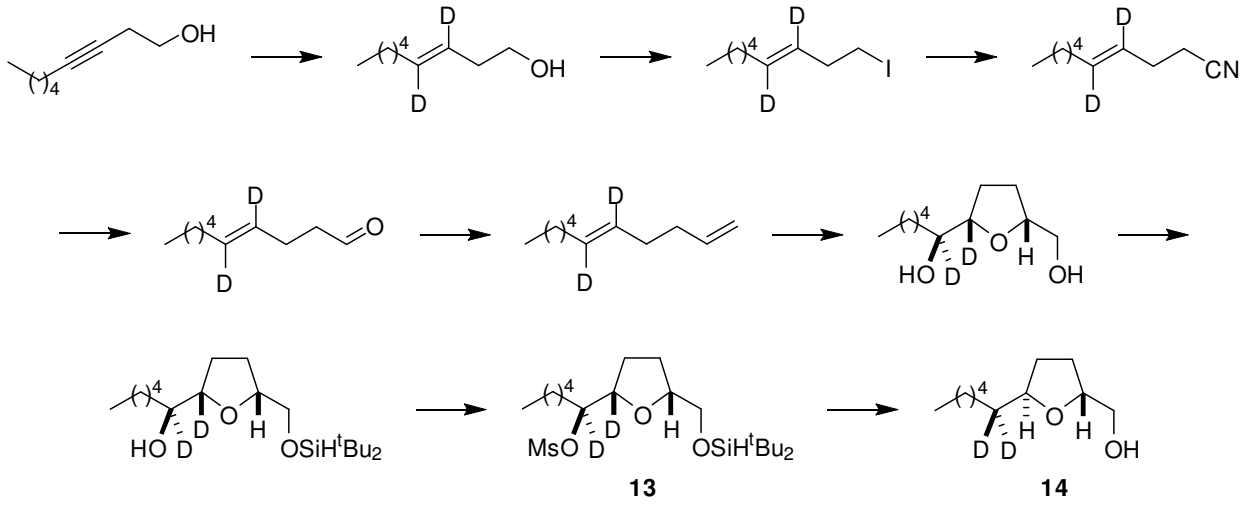


Following **General Procedure 5**, *O*-Silyl THF **12** (21 mg, 0.054 mmol) furnished the alcohol (20 mg, 92%) as a colourless oil after purification by column chromatography (petrol:acetone 200:1 to 100:1).

IR ν_{max} (film)/cm^{-1} 3446, 2929; **δ_H(500 MHz; CDCl$_3$)** 3.99-3.93 (1H, m), 3.92-3.87 (1H, m), 3.82-3.78 (1H, m, 2.08-2.01 (2H, m), 1.91-1.78 (2H, m), 1.62-1.25 (14H, m), 0.93-0.88 (6H, m); **δ_C(125.7**

MHz; $CDCl_3$) 81.5, 80.2, 71.9, 35.6, 32.3, 32.2, 31.9, 28.2, 25.8, 24.9, 22.7, 22.6, 14.0; **MS (ESI, *m/z*)** 229 ($M + H^+$, 100%); **HRMS (ESI, *m/z*)** $C_{14}H_{29}O_2$ ($M + H^+$) requires 229.2162, found 229.2164.

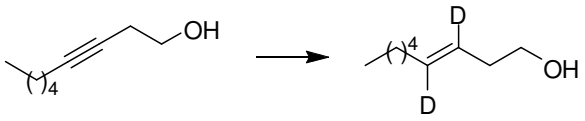
5. Synthesis of THFs 13-15



Scheme 4: Synthesis of THFs13-14

5.1 Data for starting materials and THFs 13-14

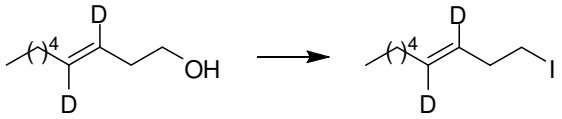
Preparation of (3*E*)-(3-$^2H_1$, 4-$^2H_1$)-non-3-en-1-ol



$LiAlD_4$ (646mg, 15.2 mmol, 2.60 eq) was carefully added to a stirred solution of non-3-yn-1-ol (820 mg, 5.86 mmol, 1.00 eq) in 1,2-dimethoxyethane (25 mL) at 0°C under an atmosphere of argon. The mixture was refluxed for 36 hours, cooled to 0°C and quenched with D_2O (10 mL). The reaction was then heated to 50°C for 45 minutes and then cooled to room temperature. The mixture was then diluted with Et_2O (150 mL), washed with 1M HCl (50 mL), and brine (50 mL), dried and concentrated onto silica. Purification by column chromatography (petrol:Et_2O 50:1) yielded the alkene (641 mg, 76%) as a yellow oil.

IR ν_{max} (film)/cm^{-1} 3346, 2926; **δ_H(400 MHz; $CDCl_3$** 3.64-3.59 (2H, m), 2.25 (2H, t, *J* 6.3), 2.00 (2H, t, *J* 7.3), 1.60-1.55 (1H, m), 1.54-1.46 (2H, m), 1.40-1.23 (6H, m), 0.88 (3H, t, *J* 6.9); **δ_C(100.6 MHz; $CDCl_3$)** 133.9 (t, *J* 22.7), 125.2 (t, *J* 22.8), 62.0, 35.8, 32.5, 31.4, 29.1, 22.5, 14.0; **MS (ESI, *m/z*)** 167 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_9H_{16}D_2ONa$ (M + Na^+) requires 167.1375, found 167.1376.

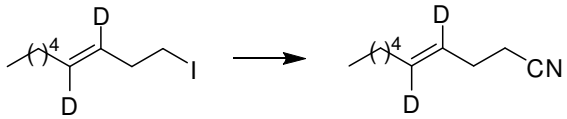
Preparation of (3*E*)-(3-$^2H_1$, 4-$^2H_1$)-iodonon-3-ene



Triphenylphosphine (2.88 g, 11.0 mmol, 1.50 eq), iodine (1.69 g, 11.0 mmol, 1.50 eq) and imidazole (992 mg, 14.7 mmol, 2.00 eq) were added to a solution of alcohol (1.05 g, 7.29 mmol, 1.00 eq) in acetonitrile:toluene (50 mL, 1:4) under an atmosphere of argon. The reaction mixture was stirred for 2 hours at 65°C before being cooled to room temperature. The mixture was diluted with Et_2O (150 mL) and washed with sodium thiosulfate (50 mL), water (50 mL) and brine (50 mL), then dried and concentrated onto silica. Purification by column chromatography (petrol:Et_2O 100:1) yielded the iodide (2.79 g, 96%) as a yellow oil.

IR ν_{max} (film)/cm^{-1} 2925; **δ_H(400 MHz; $CDCl_3$** 3.15 (2H, t, *J* 7.3), 2.55 (2H, t, *J* 6.3), 1.99 (2H, t, *J* 7.2), 1.41-1.24 (6H, m), 0.90 (3H, t, *J* 6.9); **δ_C(100.6 MHz; $CDCl_3$)** 133.2 (t, *J* 22.9), 127.8 (t, *J* 23.3), 36.8, 32.3, 31.4, 28.9, 22.5, 14.1, 6.2; **MS (ESI, *m/z*)** 254 (M^+, 100%); **HRMS (ESI, *m/z*)** $C_9H_{15}D_2I$ (M^+) requires 254.0501, found 254.0496.

Preparation of (4*E*)-(4-$^2H_1$, 5-$^2H_1$)-dec-4-enenitrile

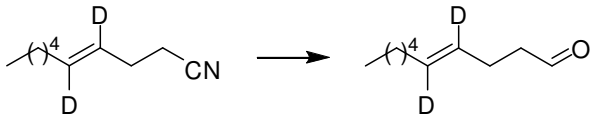


Sodium cyanide (1.26 g, 25.7 mmol, 4.00 eq) was added to a solution of iodide (1.63 g, 6.42 mmol, 1.00 eq) in acetonitrile (20 mL) under an atmosphere of argon. The reaction mixture was stirred for 72

hours at 80°C before being cooled to room temperature. The mixture was diluted with Et_2O (150 mL) and washed with sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL), then dried and concentrated onto silica. Purification by column chromatography (petrol:Et_2O 100:1) yielded the nitrile (870 mg, 89%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 2928, 2247; **δ_H(400 MHz; $CDCl_3$** 2.41-2.37 (2H, m), 2.35-2.30 (2H, m), 2.01 (2H, t, *J* 7.3), 1.41-1.23 (6H, m), 0.89 (3H, t, *J* 6.9); **δ_C(100.6 MHz; $CDCl_3$)** 133.8 (t, *J* 22.8), 125.1 (t, *J* 23.2), 119.4, 32.2, 31.3, 28.9, 28.2, 22.5, 17.1, 14.0; **MS (ESI, *m/z*)** 176 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{10}H_{15}D_2NNa$ (M + Na^+) requires 176.1379, found 176.1379.

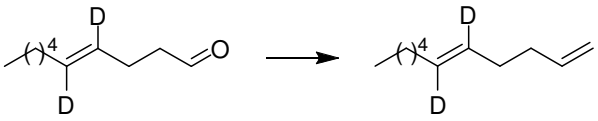
Preparation of (4*E*)-(4-$^2H_1$, 5-$^2H_1$)-dec-4-enal



DIBAL-H (1.5M in toluene) was added to a stirred solution of nitrile (585 mg, 3.82 mmol, 1.00 eq) in dichloromethane (40 mL) at -78°C under an atmosphere of argon and stirred for 1 hour. The reaction was quenched with NH_4Cl (10 mL) and allowed to warm to room temperature. The mixture was then extracted with Et_2O (3 x 50 mL). The organics were combined and washed with 1M HCl (20 mL), sodium bicarbonate (20 mL), and bine (20 mL) then dried and concentrated onto silica. Purification by column chromatography (petrol:Et_2O 50:1) yielded the aldehyde (443 mg, 74%) as a yellow oil.

IR ν_{max} (film)/cm^{-1} 1728, 2926; **δ_H(400 MHz; $CDCl_3$** 9.73 (1H, t, *J* 1.7), 2.49-2.44 (2H, m), 2.33-2.27 (2H, m), 1.95 (2H, t, *J* 7.1), 1.36-1.17 (6H, m), 0.86 (3H, t, *J* 7.0); **δ_C(100.6 MHz; $CDCl_3$)** 202.3, 131.6 (t, *J* 22.7), 127.1 (t, *J* 23.0), 43.5, 32.3, 31.3, 29.0, 22.5, 25.0, 14.0; **MS (ESI, *m/z*)** 179 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{10}H_{16}D_2ONa$ (M + Na^+) requires 179.1375, found 179.1373.

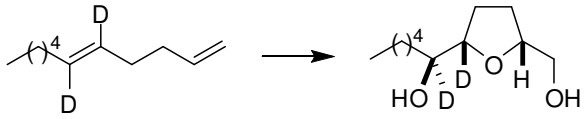
Preparation of (5*E*)-(5-$^2H_1$, 6-$^2H_1$)-undeca-1,5-diene



BuLi (1.6M in hexanes, 2.77 mL, 4.43 mmol, 2.50 eq) was added to a stirred suspension of methyl triphenylphosphonium bromide (1.58g, 4.43 mmol, 2.50 eq) in THF (20 mL) at 0°C under an atmosphere of argon and stirred for 30 minutes. The mixture was then cool to -78°C and the aldehyde (277 mg, 1.77 mmol, 1.00 eq) was added dropwise as a solution in THF (5 mL). The reaction mixture was then allowed to warm to room temperature over 16 hours and then quenched with NH_4Cl (10 mL). The mixture was then diluted with Et_2O (50 mL) and washed with water (20 mL) and brine (20 mL), dried and concentrated onto silica. Purification by column chromatography (petrol) yielded the diene (231 mg, 85%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 2923; **δ_H(400 MHz; $CDCl_3$** 5.89-5.78, 5.06-4.94 (2H, m), 2.15-2.04 (4H, m), 1.98 (2H, t, *J* 7.1), 1.40-1.23 (8H, m), 0.90 (3H, t, *J* 7.0); **δ_C(100.6 MHz; $CDCl_3$)** 138.6, 130.5 (t, *J* 22.7), 128.9 (t, *J* 22.9), 114.4, 33.9, 32.4, 32.4, 31.4, 29.3, 22.5, 14.1; **MS (FI, *m/z*)** 154 (M^+, 100%); **HRMS (FI, *m/z*)** $C_{11}H_{18}D_2$ (M^+) requires 154.1687, found 154.1691.

Preparation of (1'*RS*, 2*RS*,5*SR*)-(2-$^2H_1$, 1'-$^2H_1$)-2-(1'-hydroxyhexyl)-5-(hydroxymethyl)tetrahydrofuran

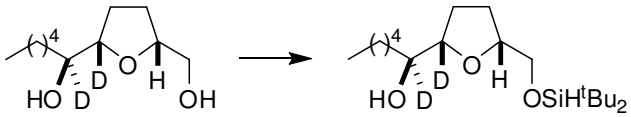


Following **General Procedure 1**, a solution of diene (237 mg, 1.54 mmol) in DCM (30 mL) yielded the THF (220 mg, 70%) as a colourless oil after purification by column chromatography (petrol:acetone 30:1 to 5:1).

IR ν_{max} (film)/cm^{-1} 3386, 2928; **δ_H(400 MHz; $CDCl_3$** 4.12-4.04 (1H, m), 3.75 (1H, dd, *J* 2.9, 11.7), 3.51 (1H, dd, *J* 5.3, 11.7), 2.92 (2H, br s), 1.96-1.89 (2H, m,), 1.84-1.69 (2H, m), 1.55-1.20 (8H, m), 0.89 (3H, dt, *J* 6.8); **δ_C(100.6 MHz; $CDCl_3$)** 82.6 (t, *J* 22.1), 79.9, 73.8 (t, *J* 21.2), 65.1, 33.9, 31.9,

28.1, 27.2, 25.3, 22.6, 14.1; **MS (ESI, *m/z*)** 227 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{11}H_{20}D_2O_3Na$ (M + Na^+) requires 227.1587, found 227.1586.

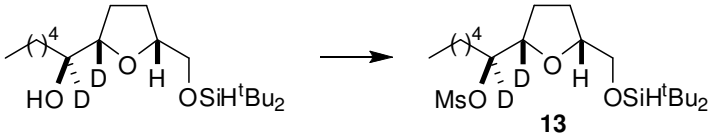
Preparation of (1'*RS*, 2*RS*, 5*SR*)-(2-$^2H_1$, 1'-$^2H_1$)-2-(1'-hydroxyhexyl)-5-(di-*tert*-butyl silyloxymethyl)tetrahydrofuran



Following **General Procedure 2**, the THF (37 mg, 0.18 mmol) in dichloromethane (2 mL) yielded *O*-Silyl THF (52 mg, 83%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 50:1).

IR ν_{max} (film)/cm^{-1} 3486, 2928, 2088; **δ_H(400 MHz; $CDCl_3$)** 4.10-4.03 (1H, m), 4.00 (1H, s), 3.84 (1H, dd, *J* 4.5, 10.6), 3.72 (1H, dd, *J* 4.1, 10.6), 2.45 (1H, br s), 1.97-1.89 (3H, m), 1.82-1.74 (1H, m), 1.56-1.21 (8H, m), 1.01 (9H, s) overlapping 1.00 (9H, s), 0.88 (3H, t, *J* 6.9); **δ_C(100.6 MHz; $CDCl_3$)** 82.1 (t, *J* 21.7), 79.9, 74.0 (t, *J* 21.6), 69.3, 34.2, 31.9, 28.1, 27.5, 27.5, 27.2, 25.4, 22.6, 20.3, 20.2, 14.1; **MS (ESI, *m/z*)** 369 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{19}H_{38}D_2O_3Si$ (M + Na^+) requires 369.2764, found 369.2772.

Preparation of (1'*RS*, 2*RS*, 5*SR*)-(2-$^2H_1$, 1'-$^2H_1$)-{5- [(di-*tert*-butyl silyloxymethyl)methyl]tetrahydrofuran-2-yl}hexyl methanesulfonate 13

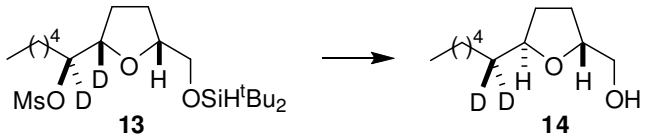


Following **General Procedure 3**, the alcohol (26 mg, 0.075 mmol) yielded mesylate **13** (27 mg, 85%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 50:1).

IR ν_{max} (film)/cm^{-1} 2936 , 2085; **δ_H(400 MHz; $CDCl_3$)** 4.09-4.03 (1H, m), 3.98 (1H, s) 3.76 (1H, dd, *J* 5.4, 10.6), 3.68 (1H, dd, *J* 5.2, 10.6), 3.14 (3H, s), 2.03-1.90 (2H, m), 1.85-1.76 (1H, m), 1.66-1.13

(9H, m), 1.00 (18H, s), 0.89 (3H, t, *J* 6.7); **δ_C(100.6 MHz; $CDCl_3$)** 86.8 (t, *J* 22.4), 80.1 (t, *J* 24.3), 80.0, 69.5, 39.9, 31.6, 31.5, 27.8, 27.7, 27.2, 24.4, 22.4, 20.2, 20.1, 14.0; **MS (ESI, *m/z*)** 447 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{20}H_{40}D_2O_5SSi$ (M + Na^+) requires 447.2540, found 447.2546.

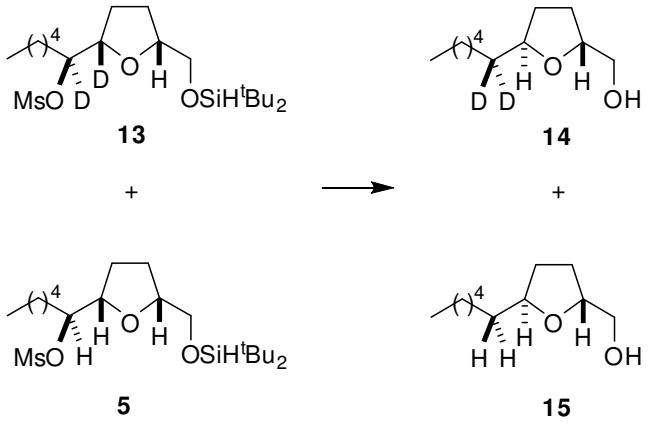
Preparation of (2*RS*, 5*SR*)-(2-$^2H_1$, 1'-$^2H_1$)-2-hexyl-5-(hydroxymethyl)tetrahydrofuran



Following **General Procedure 4**, *O*-Silyl THF **13** (16.0 mg, 0.036 mmol) was stirred at 40ºC for 72 hours yielding the *trans*-THF **14** (5.2 mg, 77%) as a colourless oil after purification by column chromatography (petrol:acetone 100:1 to 50:1).

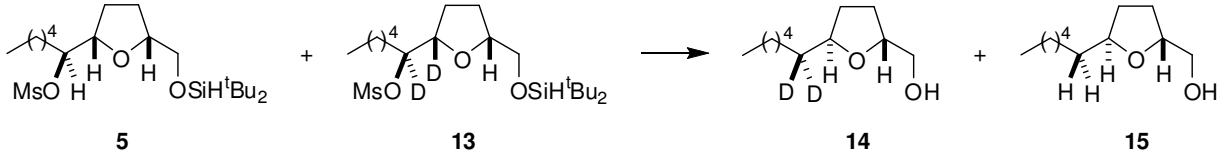
IR ν_{max} (film)/cm^{-1} 3425, 2925; **δ_H(400 MHz; $CDCl_3$)** 4.11 (1H, ddt, *J* 4.4, 6.8, 7.8), 3.92 (1H, dd, *J* 5.9, 8.0), 3.64 (1H, dd, *J* 3.3, 11.5), 3.49 (1H, dd, *J* 6.3, 11.5), 2.07-1.93 (3H, m), 1.79 (1H, br s), 1.72-1.18 (9H, m), 0.89 (3H, t, *J* 6.8); **δ_C(125.7 MHz; $CDCl_3$)** 79.4. 78.8, 65.1, 34.9 (quin., *J* 19.1,), 32.0, 31.8, 29.3, 27.5, 26.0, 22.6, 14.1; **MS (ESI, *m/z*)** 211 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{11}H_{20}D_2O_2$ (M + Na^+) requires 211.1638, found 211.1636.

5.2 Crossover experiment of 13 and 5



Scheme 5: Crossover experiment of THFs 13 and 5

Alternative preparations of (2*RS*, 5*SR*)-2-hexyl-5-(hydroxymethyl)tetrahydrofuran 15 and (2*RS*, 5*SR*)-(2-^{2}H$_1$, 1'-^{2}H$_1$)-2-hexyl-5-(hydroxymethyl)tetrahydrofuran 14

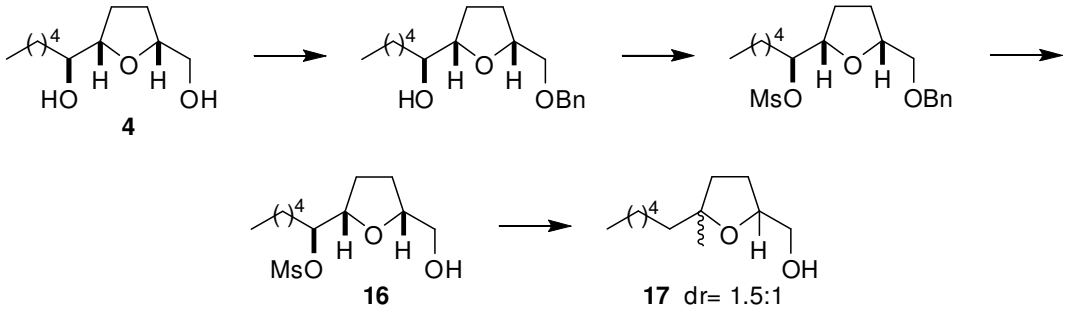


Zinc acetate (82mg, 0.45 mmol, 10.0 eq) was added to a solution of doubly-deuterated THF **13** (20.0 mg, 0.045 mmol, 1.0 eq) and non-deuterated THF **5** (6.7 mg, 0.015 mmol, 0.33 eq) in hexafluorispropanol (0.60 mL). The solution was stirred at 40ºC for 24 hours after which further non-deuterated THF **5** (6.7 mg, 0.015 mmol, 0.33 eq) in hexafluoroisopropanol (0.15 mL). This was repeated after a further 24 hours after which the reaction was stirred at 40ºC for a final 24 hours and then cooled to room temperature and diluted with EtOAc (20 mL). The mixture was then washed water (10 mL) and brine (10mL), dried and concentrated onto silica. Purification by column chromatography (petrol:acetone 100:1 to 50:1) yielded an inseparable mixture of non-deuterated THF **15** and doubly-deuterated THF **14** (11.5 mg, 50:50, 69%) as a colourless oil after purification by column chromatography (petrol:acetone 200:1 to 500:1).

δ_H(400 MHz; $CDCl_3$) 4.15-4.08 (2H, m, **14** and **15**), 3.96-3.90 (2H, m, **14** and **15**), 3.64 (1H, dd, *J* 3.3, 11.5, **14** and **15**), 3.49 (1H, dd, *J* 6.3, 11.5, **14** and **15**), 2.07-1.93 (6H, m, **14** and **15**), 1.74-1.23 (20H, m, **14** and **15**), 0.89 (3H, t, *J* 6.8, **14** and **15**); **δ_C(125.7 MHz; $CDCl_3$)** 79.5 (**15**). 79.4 (**14**), 78.7

(**14** and **15**), 65.1 (**14** and **15**), 35.7 (**15**), 34.9 (quin., *J* 19.1, **14**), 32.1 (**14** and **15**), 32.0 (**14** and **15**), 31.8 (**14** and **15**), 29.4 (**14** and **15**), 29.3 (**14** and **15**), 27.5 (**14** and **15**), 26.2 (**14** and **15**), 26.0 (**14** and **15**), 22.6 (**14** and **15**), 14.1 (**14** and **15**); **MS (ESI, *m/z*)** 209 (M(**15**) + Na^+, 100%), 211 (M(**14**) + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{11}H_{22}O_2$ (M(**15**) + Na^+, 100%) requires 209.1512, found 209.1509 and $C_{11}H_{20}D_2O_2$ (M(**14**) + Na^+, 100%) requires 211.1638, found 211.1632.

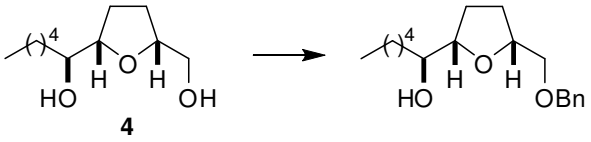
6. Synthesis of THFs 16-17



Scheme 6: Synthesis of THFs 16-17

6.1 Data for starting materials and THFs 16-17

Preparation of (1'*RS*, 2*RS*, 5*SR*)-2-(1'-hydroxyhexyl)-5-(benzyloxymethyl)tetrahydrofuran

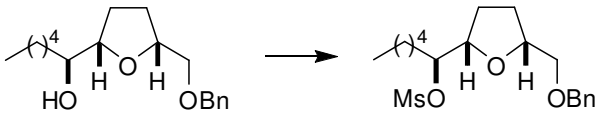


Freshly prepared Ag_2O (2.6 g, 11.2 mmol, 1.5 eq) was added to a stirred solution of alcohol **4** (1.5 g, 7.41 mmol, 1.0 eq) in toluene (40mL) under an atmosphere of argon. Benzyl bromide (1.24 mL, 10.8 mmol, 1.4 eq) was then added. The reaction was stirred for 24 hours and then concentrated onto silica to yield the mono benzylated THF (1.84 g, 85%) as a colourless oil after column chromotography (petrol:acetone 100:1 to 40:1).

IR ν_{max} (film)/cm^{-1} 3463, 2931; **δ_H(400 MHz; $CDCl_3$)** 7.36-7.24 (5H, m), 4.57 (1H, d, *J* 12.2), 4.54 (1H, d, *J* 12.2), 4.17-4.11 (1H, m), 3.86-3.80 (1H, m), 3.56 (1H, dd, *J* 4.0, 10.0), 3.45 (1H, dd, *J* 4.8, 10.0), 3.40-3.34 (1H, m), 2.80 (1H, s), 1.95-1.73 (4H, m), 1.55-1.23 (8H, m), 0.89 (3H, t, *J* 6.7);

δ_C(100.6 MHz; $CDCl_3$) 138.0, 128.4, 127.8, 127.7, 82.9, 78.4, 74.3, 73.3, 72.4, 34.2, 31.9, 28.1, 25.4, 22.7, 14.1; **MS (ESI, *m/z*)** 351 (M + MeCN + NH_4^+, 100%); **HRMS (ESI, *m/z*)** $C_{18}H_{28}O_3Na$ (M + Na^+) requires 315.1931, found 315.1930.

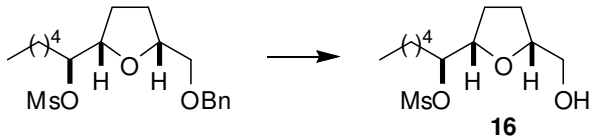
Preparation of (1'*RS*, 2*RS*, 5*SR*)-{5-[(benzyloxy)methyl]tetrahydrofuran-2-yl}hexyl methanesulfonate



Following **General Procedure 3**, the alcohol (337 mg, 1.15 mmol) yielded the mesylate (414 mg, 98%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 2955; **δ_H(400 MHz; $CDCl_3$)** 7.27-7.38 (5H, m), 4.57-4.52 (3H, m), 4.22-4.15 (1H, m), 4.05-3.98 (1H, m), 3.49-3.47 (2H, m), 3.09 (3H, s), 2.06-1.91 (2H, m), 1.81-1.72 (1H, m), 1.70-1.55 (3H, m), 1.54-1.38 (2H, m), 1.36-1.21 (4H, m), 0.90 (3H, t, *J* 6.8); **δ_C(100.6 MHz; $CDCl_3$)** 138.1, 128.4, 127.8, 127.7, 87.0, 80.6, 78.5, 73.4, 73.0, 38.8, 31.7, 31.5, 28.1, 24.6, 22.4, 14.0; **MS (ESI, *m/z*)** 429 (M + MeCN + NH_4^+, 100%), 393 (M + Na^+, 10%); **HRMS (ESI, *m/z*)** $C_{19}H_{30}O_5SNa$ (M + Na^+) requires 393.1706, found 393.1703.

Preparation of (1'*RS*, 2*RS*, 5*SR*)-[5-(hydroxymethyl)tetrahydrofuran-2-yl]hexyl methanesulfonate 16

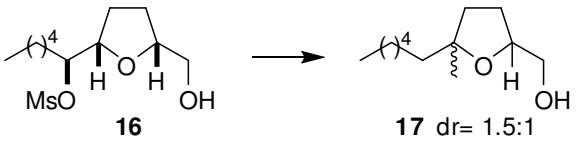


16

Benzyl ether (300 mg, 0.809 mmol) in methanol (4 mL) was treated with Pd/C (10%, spatula tip). The reaction vessel was evacuated and filled with hydrogen five times, then allowed to stir at ambient temperature under an atmosphere of hydrogen (1 atm) for 4 hours. The reaction was filtered through a pad of celite and the solvent removed *in vacu* to give mesylate **16** (223 mg, 99%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 3474, 2955; **δ_H(400 MHz; $CDCl_3$)** 4.60-4.54 (1H, m), 4.18-4.12 (1H, m), 4.08-4.01 (1H, m), 3.74 (1H, dd, *J* 3.0, 12.0), 3.53-3.48 (1H, m), 3.15 (3H, s), 2.09-1.83 (3H, m), 1.76-1.66 (1H, m), 1.65-1.56 (2H, m), 1.56-1.22 (6H, m), 0.89 (3H, t, *J* 6.4); **δ_C(100.6 MHz; $CDCl_3$)** 86.9, 80.6, 80.3, 64.5, 39.0, 31.4, 28.5, 28.0, 26.8, 24.7, 22.4, 14.0; **MS (ESI, *m/z*)** 339 (M + MeCN + NH_4^+, 100%); **HRMS (ESI, *m/z*)** $C_{12}H_{24}O_5SNa$ (M + Na^+) requires 303.1237, found 303.1238.

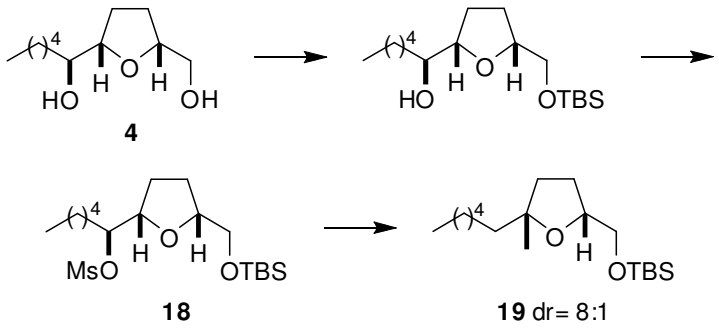
(5-methyl-5-hexyltetrahydrofuran-2-yl)methanol 17



The mesylate **16** (107 mg, 0.38 mmol) was subjected to **General Procedure 8** for 3 h to give a residue which was purified by column chromatography (petrol:acetone 9:1) to give the alcohol **17** (70 mg, 91%) as a colourless oil in a 1.5:1 ratio of diastereomers.

IR ν_{max} (film)/cm^{-1} 3424, 2930; **δ_H(400 MHz; $CDCl_3$)** 4.14-4.02 (1H, m, THF C*H*), 3.72 (1H, m), 3.51-3.44 (1H, m), 2.06-1.66 (4H, m), 1.57-1.45 (2H, m), 1.33-1.26 (8H, m), 1.20-1.19 (3H, m), 0.90-0.86 (3H, m); **δ_C(100.6 MHz; $CDCl_3$)** 83.8, 83.7, 79.0, 78.2, 65.3, 65.1, 42.0, 41.3, 36.9, 36.6, 31.9, 31.8, 29.9, 27.5, 26.8, 25.6, 24.8, 24.7, 22.6, 14.1 (q); **MS (ESI, *m/z*)** 223 (100%, M + Na^+); **HRMS (ESI, *m/z*)** $C_{12}H_{24}O_2Na$ (M + Na^+) requires 223.1669, found 223.1658.

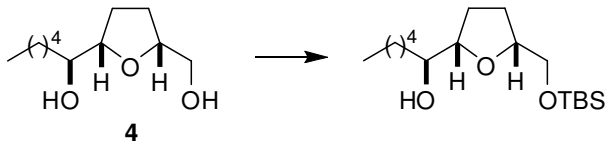
7. Synthesis of THFs 18-19



Scheme 7: Synthesis of THFs 18-19

7.1 Data for starting materials and THFs 18-19

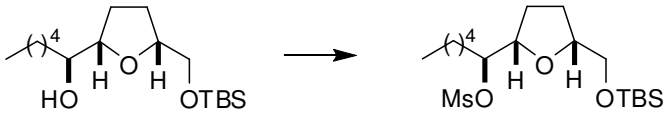
(R*)-1-((2S*,5R*)-5-((tert-butyldimethylsilyloxy)methyl)-2,5-dimethyltetrahydrofuran-2-yl)hexan-1-ol



The diol **4** (531 mg, 2.63 mmol) was subjected to **General Procedure 7** in DCM (25 mL) to give a residue which was purified by column chromatography (petrol:acetone 95:5) to give the silyl ether (700 mg, 84%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 3472, 2930; **δ_H(400 MHz; $CDCl_3$)** 4.07-4.03 (1H, m), 3.87-3.83 (1H, m), 3.75 (1H, dd, *J* 10.7 and 4.0), 3.60 (1H, dd, *J* 10.7 and 3.4), 3.39-3.33 (1H, m), 2.77 (1H, d, *J* 6.3), 1.98-1.73 (4H, m), 1.52-1.25 (8H, m), 0.91 (9H, s), 0.89 (3H, t, *J* 6.8), 0.08 (6H, s); **δ_C(100.6 MHz; $CDCl_3$)** 82.5, 79.8, 74.5, 65.2, 34.4, 31.9, 28.5, 27.3, 26.0, 25.9, 25.5, 22.6, 18.4, 14.0, -5.4, -5.5; **MS (ESI, *m/z*)** 339 (100%, M + Na^+); **HRMS (ESI, *m/z*)** $C_{17}H_{36}O_3SiNa$ (M + Na^+) requires 339.2326, found 339.2313.

(R*)-1-((2S*,5R*)-5-((tert-butyldimethylsilyloxy)methyl)tetrahydrofuran-2-yl)hexyl methanesulfonate 18

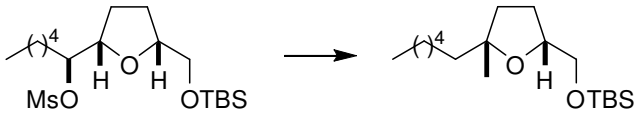


18

The alcohol (700 mg, 2.21 mmol) was subjected to **General Procedure 3** to give a residue which was purified by column chromatography (petrol:acetone 12:1) to give the mesylate **18** (703 mg, 81%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 2955, 2858, 1463; **δ_H(400 MHz; $CDCl_3$)** 4.56-4.51 (1H, m), 4.08-3.97 (2H, m), 3.58 (2H, d, *J* 4.8), 2.02-1.90 (2H, m), 1.82-1.74 (1H, m), 1.65-1.58 (3H, m), 1.51-1.44 (2H, m), 1.35-1.26 (4H, m), 0.91-0.87 (12H, m), 0.06 (6H, s) **δ_C(100.6 MHz; $CDCl_3$)** 87.2, 80.7, 80.2, 65.8, 38.9, 31.7, 31.6, 28.1, 27.7, 25.9, 24.5, 22.4, 18.3, 14.0, -5.4; **MS (ESI, *m/z*)** 417 (100%, M + Na^+), 395 (10%, MH^+); **HRMS (ESI, *m/z*)** $C_{18}H_{42}O_5SSiNa$ (M + Na^+) requires 412.2547, found 412.2547.

tert-butyldimethyl(((2R*,5R*)-5-methyl-5-hexyltetrahydrofuran-2-yl)methoxy) silane 19

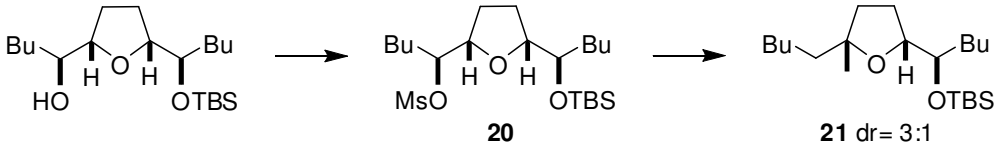


18 **19** dr= 8:1

The mesylate **18** (67 mg, 0.17 mmol) was subjected to **General Procedure 8** for 8 h to give the analytically pure silyl ether **19** (47 mg, 88%) as a colourless oil in an 8:1 ratio of diastereomers.

IR ν_{max} (film)/cm^{-1} 2930, 2858, 1463; **δ_H(400 MHz; $CDCl_3$)** *major diastereomer* 4.06-4.00 (1H, m), 3.64 (1H, dd, *J* 10.2 and 4.3), 3.50 (1H, dd, *J* 10.2 and 6.1), 2.04-1.95 (1H, m), 1.84-1.72 (1H, m), 1.64-1.60 (1H, m), 1.52-1.43 (1H, m), 1.31-1.26 (10H, m), 1.17 (3H, s), 0.90 (9H, s), 0.89 (3H, t, *J* 7.0), 0.06 (6H, s); **δ_C(100.6 MHz; $CDCl_3$)** *major diastereomer* 83.5, 78.6, 66.0, 42.1, 36.1, 31.9, 29.9, 28.3, 26.0, 25.7, 24.8, 22.6, 18.4, 14.1, -5.3, -5.4; **MS (ESI, *m/z*)** 337 (100%, M + Na^+); **HRMS (ESI, *m/z*)** $C_{18}H_{38}O_2SiNa$ requires (M+Na^+) 337.2533, found 337.2528.

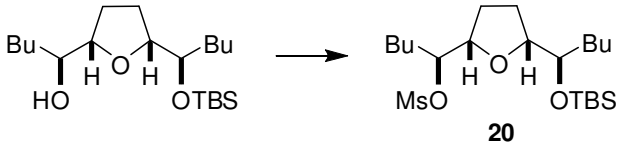
8. Synthesis of THFs 20-21



Scheme 8: Synthesis of THFs 20-21

8.1 Data for THFs 20-21

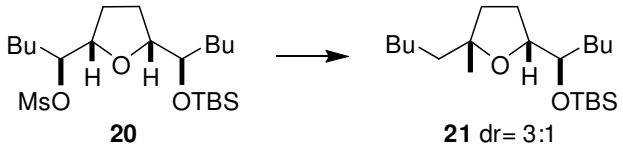
(R*)-1-((2S*,5S*)-5-((S*)-1-(tert-butyldimethylsilyloxy)pentyl)tetrahydrofuran-2-yl) pentyl methanesulfonate 20



The alcohol (300 mg, 0.84 mmol) was subjected to **General Procedure 3** to give the mesylate **20** (328 mg, 90%) as a colourless oil.

IR ν_{max} (film)/cm^{-1} 2956, 1464, 1358; **δ_H(400 MHz; $CDCl_3$)** 4.60-4.55 (1H, m), 4.02-3.93 (2H, m), 3.64-3.59 (1H, m), 3.10 (3H, s), 1.95-1.26 (16H, m), 0.93-0.88 (15H, m), 0.07 (3H, s), 0.06 (3H, s); **δ_C(100.6 MHz; $CDCl_3$)** 86.4, 81.5, 80.0, 73.9, 38.8, 32.7, 31.4, 28.2, 28.0, 26.9, 26.8, 25.9, 22.9, 22.8, 18.1, 14.1, 13.9, -4.4, -4.5; **MS (ESI, *m/z*)** 459 (100%, M + Na^+), 437 (70%, MH^+); **HRMS (ESI, *m/z*)** $C_{21}H_{44}O_5SSiNa$ (M + Na^+) requires 459.2571, found 459.2561.

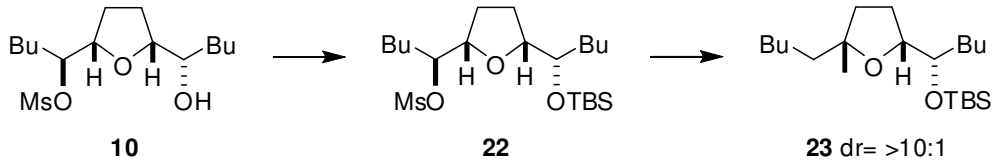
tert-butyldimethyl((R*)-1-((R*)-5-methyl-5-pentyltetrahydrofuran-2-yl) pentyloxy)silane 21



The mesylate 20 (130 mg, 0.30 mmol) was subjected to **General Procedure 8** for 8 h to give a residue which was purified by column chromatography (petrol:acetone 50:1) to give the tetrahydrofuran **21** (72 mg, 67%) as a colourless oil in a 3:1 ratio of diastereomers.

IR ν_{max} (film)/cm^{-1} 2957, 1463, 1252; **δ_H(400 MHz; $CDCl_3$)** *major diastereomer* 3.90 (1H, q, *J* 6.7), 3.64-3.60 (1H, m), 1.87-1.79 (1H, m), 1.75-1.58 (3H, m), 1.53-1.25 (14H, m), 1.15 (3H, s), 0.91-0.88 (15H, m), 0.07 (3H, s), 0.06 (3H, s); **δ_C(100.6 MHz; $CDCl_3$)** *major diastereomer* 83.0, 80.8, 74.7, 42.0, 36.6, 32.5, 31.9, 28.0, 27.1, 26.5, 26.0, 24.5, 22.7, 18.3, 14.1, 14.1, -4.2, -4.7; **MS (ESI, *m/z*)** 379 (60%, M + Na^+), 225 (100%); **HRMS (ESI, *m/z*)** $C_{21}H_{44}O_2SiNa$ (M + Na^+) 379.3003, found 379.3005.

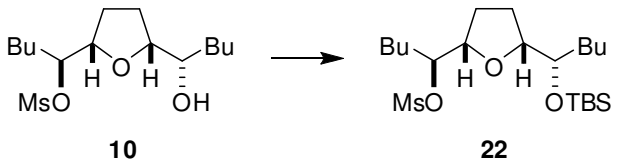
9. Synthesis of THFs 22-23



Scheme 9: Synthesis of THFs 22-23

9.1 Data for THFs 22-23

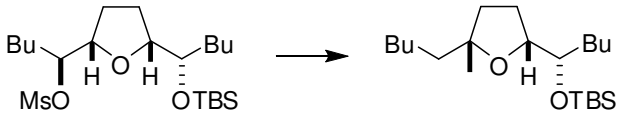
Preparation of (1'*RS*, 1"*RS*, 2*RS*, 5*SR*)-(5-{[1" *tert*-butyl(dimethyl) silyloxypentyl] tetrahydrofuran-2-yl}pentyl) methanesulfonate 22



Following **General Procedure 7** in DMF (1 mL), the alcohol **21** (60 mg, 0.388 mmol) yielded the silyl ether **22** (77 mg, 95%) as a colourless oil after column chromatography (petrol:acetone 200:1 to 50:1).

IR ν_{max} (film)/cm^{-1} 2957; **δ_H(400 MHz; $CDCl_3$)** 4.61-4.55 (1H, m), 3.92-3.82 (2H, m), 3.65-3.60 (1H, m), 3.12 (3H, s), 1.93-1.83 (3H, m), 1.65-1.58 (2H, m), 1.58-1.24 (11H, m), 0.93-0.97 (15H, m), 0.06 (6H, s); **δ_C(100.6 MHz; $CDCl_3$)** 86.6, 81.9, 80.6, 73.7, 38.8, 33.8, 31.6, 28.0, 26.9, 26.7, 26.6, 25.9, 22.9, 22.4, 18.1, 14.1, 13.8, -4.2, -4.3; **MS (ESI, *m/z*)** 459 (M + Na^+, 100%); **HRMS (ESI, *m/z*)** $C_{21}H_{44}O_5SSiNa$ (M + Na^+) requires 459.3017, found 459.3006.

Preparation of (1'*SR*, 2*RR*, 5*RR*)-*tert*-butyldimethyl-1'-(5-methyl-5-pentyltetrahydrofuran-2-yl) pentyloxy)silane 23



22 **23** dr= >10:1

Following **General Procedure 8**, after 2 hours mesylate **22** (43 mg, 0.098 mmol) gave the THF **23** (29 mg, 86%) as a colourless oil after purification by column chromatography (petrol:acetone 300:1 to 100:1).

IR ν_{max} (film)/cm^{-1} 2958; **δ_H(400 MHz; $CDCl_3$)** 3.86 (1H, dt, *J* 4.8, 7.0), 3.68-3.62 (1H, m), 1.90-1.83 (2H, m), 1.70-1.55 (2H, m), 1.55-1.23 (14H, m), 1.14 (3H, s), 0.92-0.86 (15H, m), 0.06 (6H, s); **δ_C(100.6 MHz; $CDCl_3$)** 83.0, 80.3, 73.7, 42.0, 36.6, 34.7, 32.5, 27.1, 26.4, 26.0, 24.9, 24.7, 23.0, 22.6, 18.1, 14.1, -4.2, -4.3; **MS (ESI, *m/z*)** 379 (100%, M + Na^+); **HRMS (ESI, *m/z*)** $C_{21}H_{44}O_2SiNa$ (M + Na^+) requires 379.3003, found 379.3010.

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[1] K. Miura, S. Okajima, T. Hondo, T. Nakagawa, T. Takahashi, A. Hosomi, *J. Am. Chem. Soc.* **2000**, *122*, 11348.

[2] **7** was prepared as reported in T. J Donohoe, S Butterworth, *Angewandte Chemie Int Ed. Engl.* **2003**, *42*, 948.