

**Spiroacetal Biosynthesis: ( $\pm$ )-1,7-Dioxaspiro[5.5]undecane in *Bactrocera*  
*cacuminata*, and *B. oleae* (olive fruit fly).**

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## General Methods

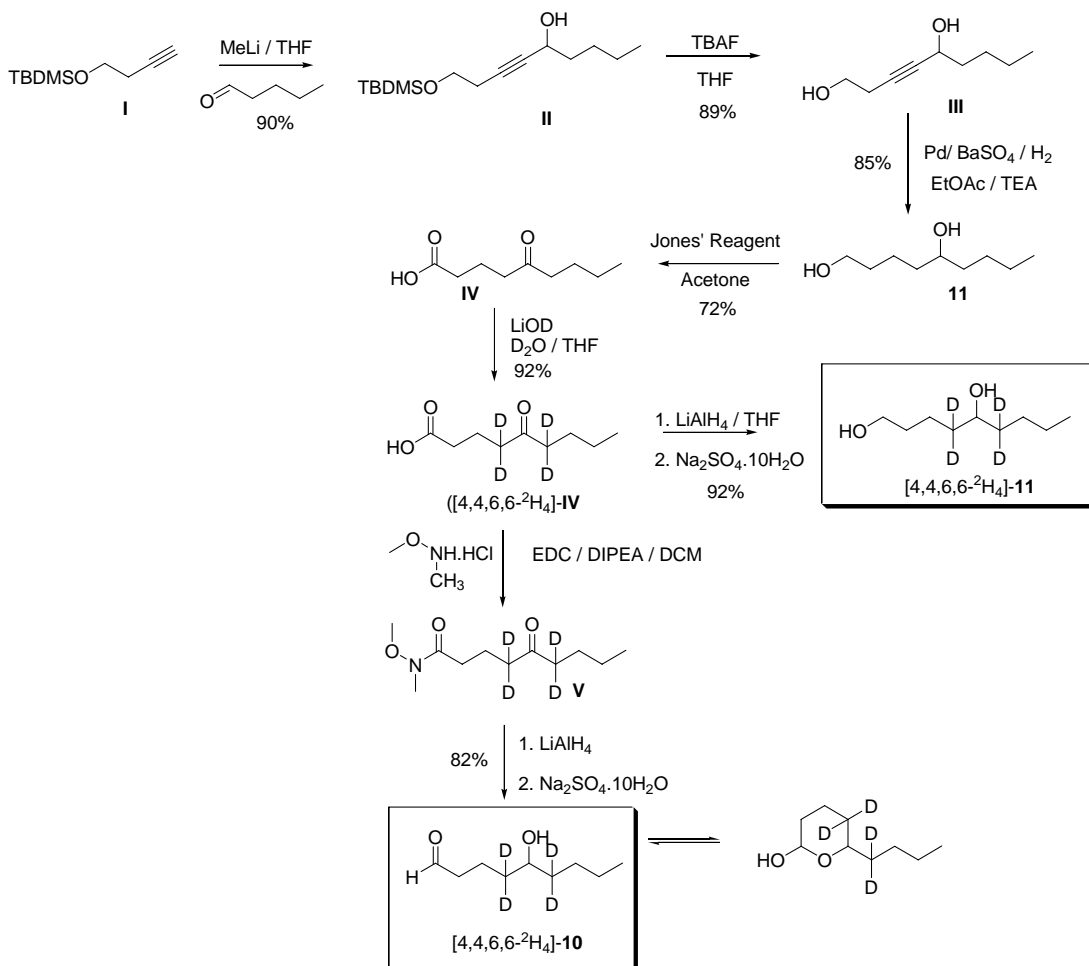
$^1\text{H}$  NMR spectra were recorded at 400 or 500 MHz with the residual  $\text{CHCl}_3$  in the  $\text{CDCl}_3$  solvent ( $\delta$  7.24 ppm) or the signal of benzene in the  $\text{C}_6\text{D}_6$  solvent ( $\delta$  7.15 ppm) as internal standards.  $^{13}\text{C}$  NMR spectra were recorded at 100 or 125 MHz with either the central peak of the  $\text{CDCl}_3$  triplet ( $\delta$  77.00 ppm) or the multiplet of benzene ( $\delta$  128.0 ppm) as internal standards. The GCMS data were recorded on a gas chromatograph – mass spectrometer at 70 eV, fitted with a 30 m  $\times$  0.25 mm BP5 column. The standard program was set as 2 minutes at 100°C, followed by a temperature increase of 16°C/min, and left for 10 min at 250°C. Flash chromatography was carried out using Merck kieselgel 60 (230 – 400 mesh) or Scharlau silica gel (200 – 400 mesh). Optical rotations were measured at sodium D line (589 nm) using a 1dm quartz cell. Enantioselective gas chromatography was conducted in the laboratory of Professor Dr. W. Koenig at the University of Hamburg by Dr. Melanie Junge with a 50% 2,6-Me-3-pe- $\gamma$  cyclodextrin stationary phase. Moisture or air sensitive experiments were conducted in oven or flame-dried glassware under an atmosphere of nitrogen. Anhydrous solvents used in moisture sensitive reactions were dried accordingly before used. THF and diethyl ether were distilled off sodium wire; DCM was distilled off  $\text{CaH}_2$ , under a nitrogen atmosphere.

## Feeding Experiments

Compounds to be fed were diluted in 150  $\mu\text{L}$  of diethyl ether and poured onto sugar to make a 5% w/w mixture. The mixture was stirred vigorously and placed under high vacuum for 30 minutes. The sugar mixture was then introduced to sexually mature males of *B. cacuminata* or females of *B. oleae* on a small piece of wax paper or wettex gauze. Over the duration of the feeding experiment head space volatile samples were taken by Solid Phase Micro Extraction (SPME) and analysed by GCMS. After 3-5 days the flies were transferred to the freezer for a few hours and then the rectal glands were excised and extracted with pentane and the extracts analysed by GCMS.

## Synthesis

### I-Synthesis of [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-5-hydroxynonanal (**10**) and [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-1,5-nonane diol (**11**)



#### (tert-Butyldimethylsilyloxy)non-3-yn-5-ol (**II**)

To a cooled solution (-10°C, salt/ice) of **I** (5 g, 27 mmol, available from protection of commercial butyn-1-ol) in THF (25 mL) was added dropwise, under nitrogen, methyl lithium (16.9 mL, 27 mmol, 1.6 M in ether). The solution was allowed to stir for 15 min at -10°C, cooled to -40°C (CH<sub>3</sub>CN/CO<sub>2</sub>) and then pentanal (2.32 g, 27 mmol,) in THF (20 mL) was added dropwise over 5 min. The reaction was allowed to warm to RT over 2 hours, quenched by pouring the reaction over ice and extracted with ether (3 x 50 mL).

The organic layers were combined, washed with brine (30 mL), dried ( $\text{MgSO}_4$ ), concentrated *in vacuo* and purified by flash chromatography eluting with EtOAc:Hexane (1:10) to yield **II** (6.56 g, 90%) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.036 (s, 3H), 0.85-0.90 (m, 12H), 1.26-1.42 (m, 4H), 1.56-1.70 (m, 2H), 2.39 (dt, 2H,  $J = 7.1, 1.9$  Hz), 3.68 (t, 2H,  $J = 7.1$  Hz), 4.27-4.33 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.3 (2C), 14.0, 18.3, 22.4, 23.1, 25.8 (3C), 27.3, 37.8, 61.9, 62.6, 82.2, 82.5. GC/MS EI m/z(%) 213 ( $\text{M}^+ - 57$ , 2.5), 195 (3.6), 183 (0.2), 171 (0.5), 157 (0.9), 105 (28.4), 93 (13.1), 75 (100), 57 (12.8), 41 (26.0). Anal. Calcd for  $\text{C}_{15}\text{H}_{30}\text{O}_2\text{Si}$ : C, 66.61; H, 11.18; Found: C, 66.80; H, 11.64.

### Non-3-yne-1,5-diol (**III**)

To a solution of **II** (5.0 g, 18.5 mmol) in THF (30 mL) was added TBAF (22.2 mL, 22.2 mmol, 1 M in THF) and the mixture allowed to stir overnight. The reaction was then concentrated *in vacuo*. The residue was diluted with EtOAc (150 mL) and washed with HCl (2 x 20 mL, 5%),  $\text{CuSO}_4$  (2 x 20 mL, 5%) and brine (25 mL). The organic layer was dried ( $\text{MgSO}_4$ ), concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with EtOAc:Hexane (1:1), to afford diol **III** as a colorless oil (2.57 g 89 %).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t, 3H,  $J = 6.4$  Hz), 1.55-1.71 (m, 2H,  $J = 7.6$  Hz), 2.43 (tt, 2H,  $J = 6.0, 1.7$  Hz), 3.68 (dt, 2H,  $J = 6.1, 1.1$  Hz), 4.30 (tq, 1H,  $J = 6.6, 1.9$  Hz).  $^{13}\text{C}$  NMR (100 MHz  $\text{CDCl}_3$ )  $\delta$  14.0, 22.3, 22.9, 27.3, 37.6, 60.8, 62.4, 82.0, 83.2. GC/MS EI m/z (%) 156 ( $\text{M}^+$ , 0.2), 138 (0.5), 123 (0.3), 96 (0.7), 85 (10.4), 69 (12.2), 57 (12.9), 52 (100), 41 (55.1). GC/MS EI as the di-TMS ether m/z (%) 300 ( $\text{M}^+$ , 0.2), 285 (0.4), 243 (84), 195 (1.3), 153 (7.3), 147 (36.2), 103 (21.6), 73 (100).

### 1,5-Nonane diol<sup>1</sup> (**11**)

Palladium (cat., 5% on  $\text{BaSO}_4$ ) was added to a solution of alkyne **III** (1.5 g, 5 mmol) in EtOAc (20 mL) and TEA (1 mL) and left to stir under a hydrogen atmosphere (1 atm). After 45 minutes the mixture changed colour from brown to black at which time GC/MS analysis revealed reduction was complete. The product was filtered through a bed of Celite™ concentrated *in vacuo* and purified by flash chromatography on silica gel (EtOAc:Hex, 1:1) to furnish **11** as a colorless oil (1.31 g, 85 %).  $^1\text{H}$  NMR (400 MHz,

CDCl<sub>3</sub>)  $\delta$  0.86 (t, 3H,  $J = 7.2$  Hz), 1.2-1.6 (m, 12H), 2.3 (s br, 2OH), 3.57 (m br, 1H), 3.62 (t br, 2H,  $J = 6.16$  Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  14.0, 21.7, 22.7, 27.8, 32.5, 36.9, 37.2, 62.6, 71.8. GC/MS EI m/z (%) 159 (M<sup>+</sup>-1, 0.04), 140 (0.5), 129 (0.1), 117 (6.7), 103 (11.0), 85 (88.0), 69 (73.5), 57 (74.7), 43 (59.2), 41 (100).

### 5-Oxononanoic Acid<sup>2</sup> (IV)

To a solution of 1,5-nonane diol **11** (900 mg, 5.77 mmol) in acetone (10 mL) at -10°C was added sufficient Jones' reagent (~ 1 mL) dropwise that left a persistent yellow tint after 30 min. 2-Propanol was added dropwise until the mixture turned green then acetone (30 mL) was added and the mixture subsequently filtered through a pad of Celite<sup>TM</sup>. The solution was concentrated *in vacuo* and the residue purified on silica (EtOAc:Hexane, 1:1) to give the title compound **IV** (697 mg, 72%) as colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.87 (t, 3H,  $J = 7.3$  Hz), 1.27 (sextet, 2H,  $J = 7.3$  Hz), 1.52 (pentet, 2H,  $J = 7.3$  Hz), 1.88 (pentet, 2H,  $J = 7.3$  Hz), 2.36 (t, 2H,  $J = 7.3$  Hz), 2.37 (t, 2H,  $J = 7.3$  Hz), 2.47 (t, 2H,  $J = 7.2$  Hz). <sup>13</sup>C NMR (125 MHz CDCl<sub>3</sub>)  $\delta$  13.8, 18.5, 22.3, 25.9, 33.0, 41.3, 42.6, 179.2, 210.5. GC/MS EI m/z (%) (methyl ester) 187 (M<sup>+</sup>+1, 0.3), 157 (0.7), 144 (49.6), 129 (35.8), 127 (19.1), 112 (68.0), 101 (79.8), 97 (15.6), 85 (78.3), 59 (88.4), 57 (100), 55 (78.4), 41 (79.3).

### [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-5-Oxononanoic Acid ([4,4,6,6-<sup>2</sup>H<sub>4</sub>]-IV)

Lithium granules (300 mg, 43 mmol) were added slowly (CAUTION) to D<sub>2</sub>O (10 mL) and left to cool under a nitrogen atmosphere. Keto acid **IV** (100 mg, 0.58 mmol) was then added in THF (1 mL) and left to stir for 4 days. The mixture was carefully acidified with ice cold HCl (0.05 M) and quickly extracted into chilled EtOAc (2 x 30 mL). (Alternatively CH<sub>3</sub>COOD (slight excess) was used for small scale workups to limit D-H exchange.) The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo* and purified as for **IV** to afford [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-**IV** as a colourless solid (94 mg, 92 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.89 (t, 3H,  $J = 7.4$  Hz), 1.28 (m, 2H,  $J = 7.7$  Hz), 1.53 (t br, 2H,  $J = 7.6$  Hz), 1.88 (t br, 2H,  $J = 7.12$  Hz), 2.38 (t br, 2H,  $J = 7.24$  Hz), 9.7 (s br, OH). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>)  $\delta$  13.8, 18.4, 22.2, 25.8, 32.9, 40.6 (quintet,  $J = 19.3$  Hz), 41.9 (quintet,  $J = 19.3$  Hz), 179.0, 210.9. GC/MS EI m/z (%) (methyl ester) M<sup>+</sup>+1 191

(0.2), 159 (12.5), 148 (22.8), 131 (25.4), 116 (25.5), 103 (36.0), 87 (48.9), 75 (5.5), 59 (100), 55 (19.2), 42 (22.6).

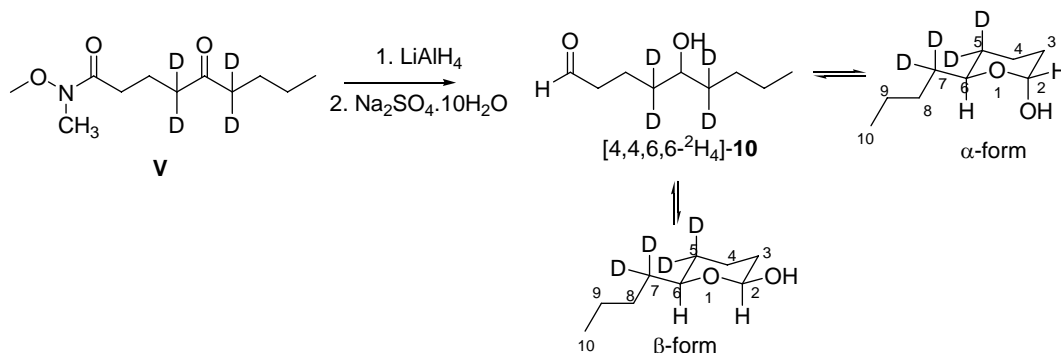
**[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-N-methoxy-N-methyl-5-oxononanamide (V)**

TEA (47.5 mg, 0.47 mmol) was added to a suspension of EDC (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (90 mg, 0.47 mmol) in DCM (5 mL), stirred for 1 minute and then acid [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-IV (82 mg, 0.47 mmol) was added in one portion followed by HOBt (63 mg, 0.47 mmol). The reaction was stirred for 45 min and then a solution of *N,O*-dimethylhydroxylamine hydrochloride (62 mg, 0.64 mmol) and TEA (65 mg, 0.64 mmol) in DCM (2 mL) was added by pipette. The coupling reaction was allowed to stir overnight and then diluted with DCM (60 mL), washed with NaHCO<sub>3</sub> (15%, 3 x 15 mL) and brine (20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo* and the residue purified on silica (EtOAc:Hexane, 1:5) to give **V** as a colorless paste (67 mg, 65 %).

**(Unlabeled)-V:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.80 (t, 3H, *J* = 7.4 Hz), 1.20 (sextet, 2H, *J* = 7.3 Hz), 1.45 (quintet, 2H, *J* = 7.6 Hz), 1.80 (quintet, 2H, *J* = 7.2 Hz), 2.30 (t, 2H, *J* = 7.4 Hz), 2.35 (br t, 2H, *J* = 7.1 Hz), 2.4 (t, 2H, *J* = 7.1 Hz), 3.07 (s, 3H), 3.58 (s, 3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>) δ 13.7, 18.5, 22.2, 25.8, 30.7 (br) & 32.0 (br), 41.6, 42.3, 61.0, 173.9 (br), 210.7. GC/MS EI *m/z* (%) 216 (M<sup>+</sup>+1, 0.1), 186 (0.1), 173 (0.9), 155 (70.3), 127 (76.9), 103 (3.4), 85 (51.3), 71 (17.7), 61 (40.2), 57 (100), 55 (82.2), 42 (34.4), 41 (52.1).

**(Labeled)-V, [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-V:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.81 (t, 3H, *J* = 7.3 Hz), 1.22 (m, 2H, *J* = 7.3 Hz), 1.44 (t br, 2H, *J* = 7.34 Hz), 1.80 (t br, 2H, *J* = 7.0 Hz), 2.36 (t br, 2H, *J* = 7.0 Hz), 3.08 (s, 3H), 3.59 (s, 3H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>) δ 13.7, 18.3, 22.1, 25.6, 30.7 (br), 31.7 (br), 31.97, 40.67-41.80 (m br, 2CD<sub>2</sub>, *J* = 19.4 Hz), 65.0, 173.7, 210.87 & 210.97 & 211.04 (C=O: 2D, 3D, 4D). GC/MS EI *m/z* (%) 220 (M<sup>+</sup>+1, 0.2), 190 (0.2), 177 (0.92), 159 (78.6), 147 (0.34), 131 (99.6), 87 (64.9), 74 (15.8), 59.2 (100), 55 (97.0), 42 (75.2).

**[5,5,6,6-<sup>2</sup>H<sub>4</sub>]-6-butyl-tetrahydro-2H-pyran-2-ol [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-10 and (unlabeled) 6-butyl-tetrahydro-2H-pyran-2-ol 10<sup>3</sup>**



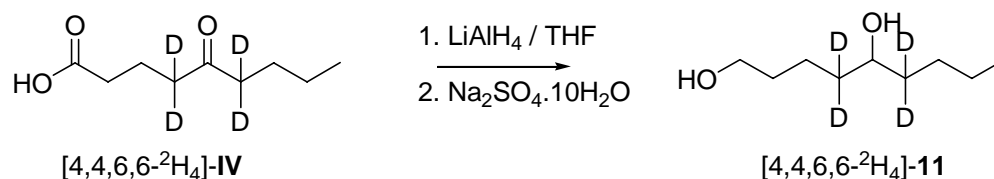
To a mixture of LiAlH<sub>4</sub> (9 mg, 0.24 mmol) in anhydrous THF (7 mL) at -10°C under nitrogen was added via syringe Weinreb amide **V** (53 mg, 0.24 mmol) in THF (3 mL). The reaction was left stirring for 30 min and then Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O (300 mg, excess) was added cautiously. After the suspension turned from grey to white the mixture was filtered through a bed of Celite<sup>TM</sup> and the filtrant was washed with ether. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography eluting with EtOAc:Hexane (1:5) to afford [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-10 (32 mg, 82%) as a colorless oil.

**(Unlabeled)-10:** <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 0.90 (t, 3H, *J* = 7.3 Hz), 0.91 (s, 3H, *J* = 7.4 Hz), 0.92-1.01 (m, 2H), 1.07-1.61 (m, 20H), 1.61-1.70 (m, 1H, H<sub>3α</sub>), 1.90 (m, 1H, H<sub>4β</sub>), 1.98 (s br, 1H, OH<sub>β</sub>), 2.61 (s br, 1H, OH<sub>α</sub>), 3.12 (dddd, 1H, *J* = 2.1; 4.7; 7.0 and 9.6 Hz, H<sub>6β</sub>), 3.90 (dddd, 1H, *J* = 2.1; 4.7; 6.9 and 7.3 Hz, H<sub>6α</sub>), 4.45 (d, 1H, *J* = 8.9 Hz, H<sub>2β</sub>), 5.10 (s, 1H, H<sub>2α</sub>). <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 14.30 and 14.34 (C<sub>10α</sub> and C<sub>10β</sub>), 17.9 (C<sub>4β</sub>), 22.4 (C<sub>4α</sub>), 23.13 and 23.16 (C<sub>9α</sub> and C<sub>9β</sub>), 28.06 and 28.09 (C<sub>8α</sub> and C<sub>8β</sub>), 30.4 (C<sub>3β</sub>), 30.8 and 31.7 (C<sub>5α</sub> and C<sub>5β</sub>), 33.3 (C<sub>3α</sub>), 36.2 and 36.4 (C<sub>7α</sub> and C<sub>7β</sub>), 68.3 (C<sub>6α</sub>), 76.1 (C<sub>6β</sub>), 91.8 (C<sub>2α</sub>), 96.8 (C<sub>2β</sub>). GC/MS EI *m/z* (%): 158 (M<sup>+</sup>, 0.5), 140 (8.7), 130 (0.2), 112 (5.0), 101 (17.7), 84 (28.4), 83 (35.9), 69 (75.6), 57 (100), 56 (75.3), 55 (95.2), 42 (44.7), 41 (93.9).

**(Labeled) [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-10:** <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 0.90 (t, 3H, *J* = 7.1 Hz), 0.91 (s, 3H, *J* = 7.1 Hz), 1.09-1.15 (m, 1H, H<sub>4α</sub>), 1.24-1.48 (m, 7H), 1.60-1.64 (m, 1H, H<sub>3β</sub>), 1.67-1.72 (m, 1H, H<sub>3α</sub>), 1.87-1.93 (m, 1H, H<sub>4β</sub>), 2.60 (s br, 1H, OH<sub>α</sub>), 3.39 (s br, 1H, OH<sub>β</sub>), 3.12 (s, 1H, H<sub>6β</sub>), 3.93 (s, 1H, H<sub>6α</sub>), 4.50-4.54 (m, H<sub>2β</sub>), 5.18 (s, 1H, H<sub>2α</sub>). <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 14.30 and 14.34 (C<sub>10α</sub> and C<sub>10β</sub>), 17.7 (C<sub>4β</sub>), 22.2 (C<sub>4α</sub>), 23.07 and 23.11

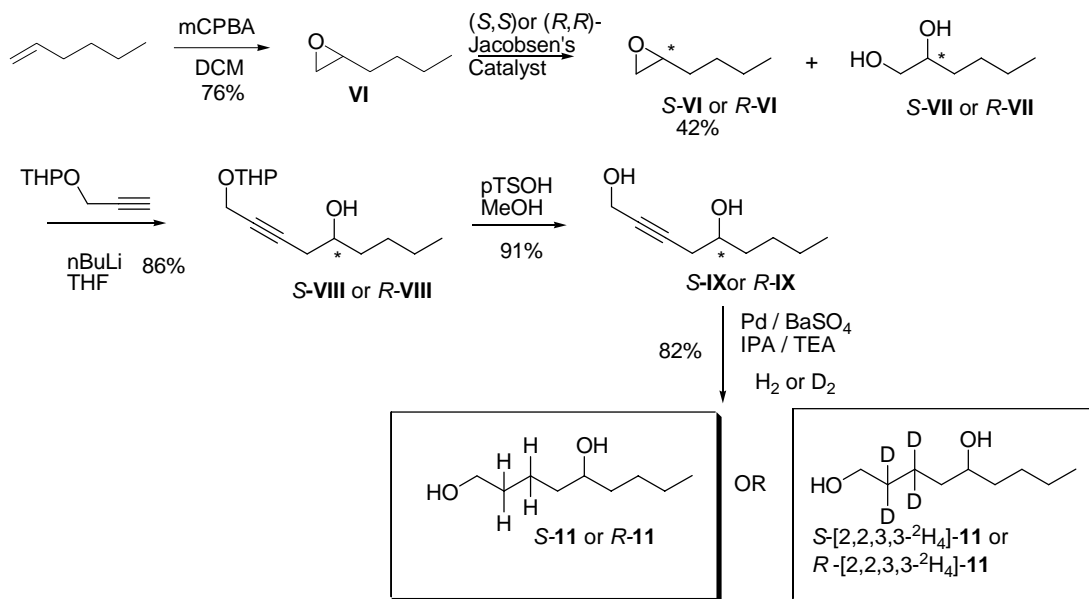
(C<sub>9α</sub> and C<sub>9β</sub>), 27.8 and 27.85 (C<sub>8α</sub> and C<sub>8β</sub>), 29.7-31.0 (m, 2C, C<sub>5α</sub> and C<sub>5β</sub>), 30.4 (C<sub>3β</sub>), 33.2 (C<sub>3α</sub>), 35.2 and 36.0 (C<sub>7α</sub> and C<sub>7β</sub>), 68.2 (C<sub>6α</sub>), 76.0 (C<sub>6β</sub>), 91.8 (C<sub>2α</sub>), 96.9 (C<sub>2β</sub>). GC/MS EI m/z(%) 162 (M<sup>+</sup>, 0.4), 144 (7.8), 132 (2.2), 116 (4.9), 103 (17.3), 87 (22.2), 71 (55.2), 58 (83.8), 57 (100), 44 (41.4), 43 (51.3). HRMS Calc: 162.1558 Found: 162.1557

**[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-1,5-Nonane diol [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-11**



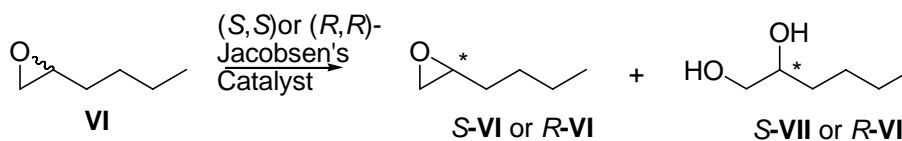
To a suspension of LiAlH<sub>4</sub> (18 mg, 0.50 mmol) in anhydrous THF (15 mL) at 0°C under nitrogen was added dropwise a solution of ketoacid **[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-IV** (55 mg, 0.31 mmol) in THF (5 mL). The reaction was allowed to warm to room temperature overnight, then cooled to 0°C and Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O (1 g, excess) was added cautiously portion-wise over 10 min. The reaction was stirred for a further hour at which time the grey mixture had turned white. This was diluted with EtOAc (50 mL), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc:Hexane, 1:1) to give **[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-11** (92 %) as a viscous colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.90 (t, 3H, *J* = 7.1 Hz), 1.30-1.64 (m, 8H), 2.03 (br s, 2OH), 3.58 (s, 1H), 3.65 (t, 2H, *J* = 6.3 Hz). <sup>13</sup>C NMR (125 MHz CDCl<sub>3</sub>) δ 14.0, 21.6, 22.7, 27.6, 32.5, 35.6-36.6 (m, 2C, *J* = 19.4), 62.6, 71.6. GC/MS EI m/z (%) 164 (M<sup>+</sup>, 0.1), 144 (0.6), 136 (0.2), 119 (7.8), 105 (14.2), 89 ( ), 87 (77.3), 71 (84.8), 58 (100), 43 (90.4), 42 (74.2), 41 (48.4).

## II- Synthesis of *R* and *S*-1,5-nonanediol (**11**), labeled and unlabeled



### 2-Butyloxirane (Hexene oxide) (**VI**)

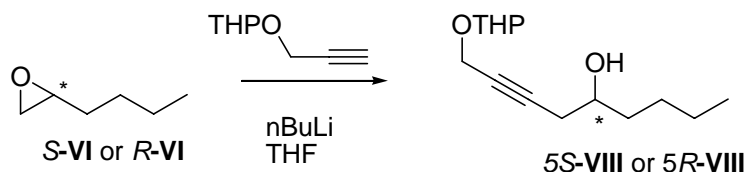
1-Hexene (10mL, 80.5 mmol) was chilled to -10°C (salt/ice) in DCM (250 mL) and mCPBA (23.8g, 80 mmol, 70% w/w) in DCM (150 mL) was added dropwise over 2 hours. The reaction was left to stir for 8 hours, filtered and then stirred vigorously with sodium sulphite (50 mL, 5% aqueous) for 5 min. The organic layer was separated and washed with NaHCO<sub>3</sub> (3 x 50 mL) and brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* carefully to give a colorless oil. The crude product was distilled (118°C, 760 mm Hg Lit.<sup>4</sup> 117-119°C 750 mmHg) to give **VI** (6.14g, 76%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.87 (t, 3H, *J* = 7 Hz), 1.2-1.6 (m, 6H), 2.4 (dd, 1H, *J* = 5.0, 2.8 Hz), 2.7 (dd, 1H, *J* = 5.0, 4.0 Hz), 2.9 (m, 1H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>) δ 13.9, 22.5, 28.1, 32.1, 47.1, 52.3.

**(S) and (R)-2-Butyloxirane (VI)**

Representative procedure for (S)-**VI**:

(*S,S*)-Jacobsen's catalyst<sup>5</sup> (*[(S,S)-N,N'*-bis(3,5-di-*tert*butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II)) (50 mg, 0.2 mol%, 0.83 mmol) was dissolved in toluene (10mL) and acetic acid added (10 mg, 0.4 mol%, 0.17 mmol) and left to stir in an unsealed flask. After one hour the toluene and excess acetic acid were removed *in vacuo* and hexene oxide (*S*)-**VI** (4.12 g, 42 mmol) was then added and the flask cooled to -10°C. Water (410  $\mu$ L, 0.55 eq, 22.8 mmol) was added at such a rate that the reaction temperature did not exceed 15°C (1 hour) and the mixture left to stir for 2 days. (*S*)-**VI** was distilled (118 °C 760 mm Hg) from the orange mixture to give a colorless oil (1.76 g, 42%) with spectral data matching that for of ( $\pm$ )-**VI**. (*S*)-**VI**  $[\alpha]_{\text{D}}^{20}$  - 10.6° (*c* 2.0 CDCl<sub>3</sub>) {lit.<sup>6</sup>  $[\alpha]_{\text{D}}^{20}$  - 10.7° (*c* 1.26, CHCl<sub>3</sub>)}.

(*R*)-**VI** was synthesized following the same procedure but with (*R,R*)-Jacobsens catalyst, with spectral data matching that for ( $\pm$ )-**VI**.  $[\alpha]_{\text{D}}^{20}$  + 10.7 (*c* 2.6, CDCl<sub>3</sub>) {lit.<sup>7</sup>  $[\alpha]_{\text{D}}^{20}$  + 9.1° (*c* 1, CHCl<sub>3</sub>)}.

**(5S and 5R)-1-(Tetrahydro-pyran-2-yloxy)-non-2-yn-5-ol (VIII)**

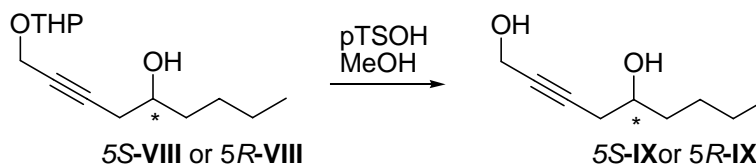
Representative procedure for (5S)-**VIII**:

A solution of THP-protected propargyl alcohol (0.7g, 5.0 mmol, available from commercial propargyl alcohol) in THF (15 mL) was cooled to -40°C (CO<sub>2</sub>/EtOH/H<sub>2</sub>O) and *n*-butyl lithium (3.4 mL, 4.8 mmol, 1.4M) was added dropwise. The reaction was then allowed to warm to RT over 2 hours, cooled to -40°C and (*S*)-**VIII** (0.4 g, 4 mmol)

in THF (15 mL) were added dropwise followed by freshly distilled boron trifluoride etherate (0.56 g, 4.0 mmol). Stirring at  $-40^{\circ}\text{C}$  was permitted for a further 2 hours and then the reaction was poured over ice/ $\text{NaHCO}_3$  and extracted into ether (3 x 50 mL). The organic layers were combined, washed with brine (30 mL) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with EtOAc:Hexane (1:5) to give **5S-VIII** as a colorless oil (0.82 g, 86%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t, 3H,  $J = 6.9$  Hz), 1.28-1.7 (m br, 10H), 1.96 (s br, OH), 2.28-2.31 (ddt, 1H,  $J = 16.6, 6.9, 2.2$ Hz), 2.40-2.46 (ddt, 1H,  $J = 16.7, 4.4, 2.0$  Hz), 3.48-3.53 (m, 1H), 3.7 (tt, 1H,  $J = 6.6, 4.8$  Hz), 3.79-3.85 (m, 1H), 4.19 (dt, 1H,  $J = 15.5, 2.1$ ), 4.26 (dt, 1H,  $J = 15.4, 2.2$ ), 4.78 (t, 1H,  $J = 3.4$  Hz).  $^{13}\text{C}$  NMR (100 MHz  $\text{CDCl}_3$ )  $\delta$  13.9, 19.1, 22.6, 25.3, 27.7, 27.8, 30.3, 36, 54.65, 54.66, 62.03, 62.04, 70.0, 78.5, 82.9, 96.91, 96.94. GC/MS EI  $m/z$  (%) 239 ( $\text{M}^+ - 1$ , 0.06), 183 (0.22), 171 (0.26), 156 (0.54), 138 (0.90), 121 (0.64), 101 (37.6), 85 (100), 69.1 (41.8), 67 (21), 52 (49.9).

(**5R**)-**VIII** was synthesized following the same procedure, with spectral data matching that for (**5S**)-**VIII**.

**(5S and 5R)-Non-2-yne-1,5-diol (IX)**



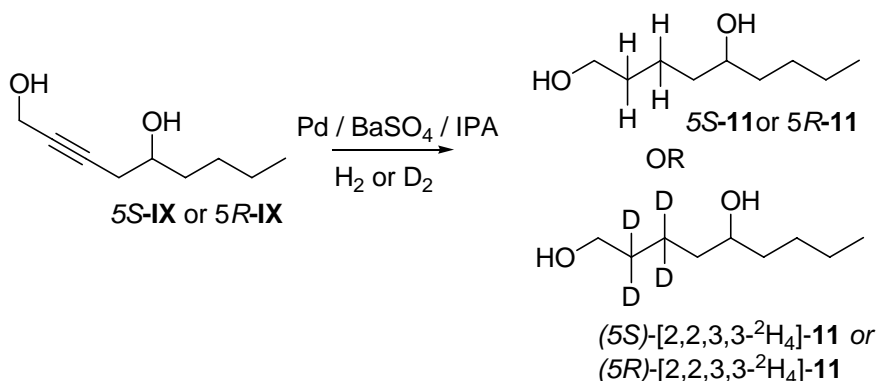
Representative procedure for (**5S**)-**IX**:

Protected alcohol (**5S**)-**VIII** (0.3 g, 1.25 mmol) was dissolved in methanol (20mL) and *p*-toluenesulfonic acid (12 mg, 0.063 mmol) was added and the reaction monitored by TLC. After two hours the reaction was complete and  $\text{NaHCO}_3$  (sat. 5 mL) was added and the methanolic solution concentrated *in vacuo*. The residue was then purified by flash chromatography, eluting with EtOAc:Hexane (1:5) which afforded **S-IX** as a colorless oil (0.18g, 91%) (*S*) isomer  $[\alpha]_{\text{D}}^{23} +8.3$  (c 1.3,  $\text{CDCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 (t, 3H,  $J = 6.9$  Hz), 1.28-1.38 (m, 4H), 1.48-1.52 (m, 2H), 2.31 (ddt, 1H,  $J = 14.5, 7.0, 2.1$  Hz), 2.38 (s br, OH), 2.44 (d quintet, 1H,  $J = 16.7, 4.4, 2.1$  Hz), 3.72 (, 1H,  $J = \text{Hz}$ ), 4.24

(t, 2H,  $J = 2.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz  $\text{CDCl}_3$ )  $\delta$  14.0, 22.6, 27.6, 27.8, 36.0, 51.2, 70.0, 80.8, 82.7. GC/MS EI  $m/z$  (%) 138 ( $\text{M}^+ - 18$ , 0.22), 123 (0.08), 109 (0.4), 95 (1.2), 85 (19.2), 69 (18.5), 57 (18.2), 52 (100).

(5*R*)-**IX** was synthesized following the same procedure, with spectral data matching that for (5*S*)-**IX** except for the optical rotation: (*R*) isomer  $[\alpha]_{\text{D}}^{23} -8.2$  ( $c$  0.9,  $\text{CDCl}_3$ ).

**(5*S* and 5*R*) 1,5-Nonane diol **11** and (5*S* and 5*R*)-[2,2,3,3- $^2\text{H}_4$ ]-1,5-Nonane diol (**11**)**



Representative procedure for (5*S*)-**11**:

(5*S*)-**IX** (34 mg, 0.22 mmol) was dissolved in a solution of IPA (5 mL) and TEA (0.5 mL) and Pd/ $\text{BaSO}_4$  (5mg) was added. The flask was twice evacuated and purged with nitrogen and then evacuated and filled with either  $^2\text{H}_2$  or  $\text{H}_2$  by balloon. After 10 min the heterogeneous mixture turned from orange to black and after 6 hours the flask was evacuated and purged with nitrogen. The mixture was filtered through Celite, concentrated *in vacuo* and purified by flash chromatography eluting with EtOAc:Hex (1:5) to give the title product (5*S*)-**11** (29 mg, 82%) as a viscous oil. Spectral data were identical to that for racemic **11**.

(5*R*)-**11** was synthesized following the same procedure, with spectral data matching that for racemic **11**.

(5*S*)-[2,2,3,3- $^2\text{H}_4$ ]-**11** and (5*R*)-[2,2,3,3- $^2\text{H}_4$ ]-**11** were synthesized following the same procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 (t, 3H,  $J = 7.0$  Hz), 1.23-1.49 (m, 8H), 1.69 (br s, 2OH), 3.56-3.61 (m, 1H), 3.63-3.64 (m, 2H).  $^{13}\text{C}$  NMR (125 MHz  $\text{CDCl}_3$ )  $\delta$  14.1, 20.6-21.4 (m), 22.8, 27.9, 31.4-32.1 (m), 36.7-36.8 (m), 37.2, 62.6 (m), 71.78 (m). GC/MS EI  $m/z$  (%) 164 ( $\text{M}^+$ , 0.02), 145 (0.3), 117 (9.7), 107 (7.0), 89 (58.7), 88 (36.9),

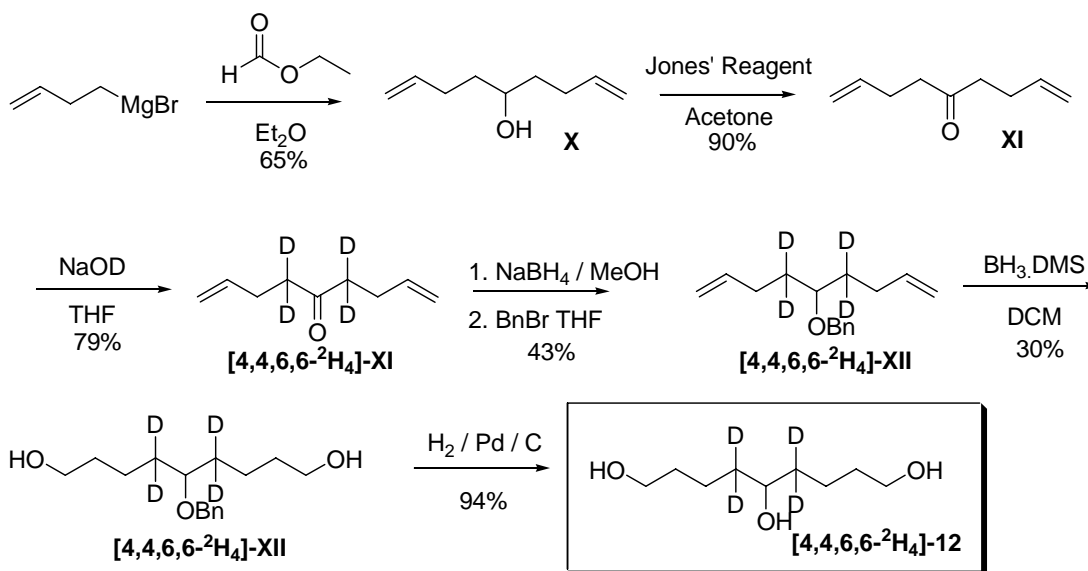
87 (47.7), 69 (100), 61 (30.2), 60 (50.7), 59 (42.9), 57 (36.6), 44 (72.7), 43 (57.6), 41 (62.4).

Enantiomeric excesses of labeled and unlabeled **11** were determined by enantioselective gas chromatography as the free alcohols and the TFA acetates. (120°C isothermal, 25 m 50% 2,6-Me-3-pe-γ).

( <i>R</i> )-1,5-nonane diol <b>11</b>	ee
Unlabeled	95.5
[2,2,3,3- <sup>2</sup> H <sub>4</sub> ]-	98.7

( <i>S</i> )-1,5-nonane diol <b>11</b>	ee
Unlabeled	95.9
[2,2,3,3- <sup>2</sup> H <sub>4</sub> ]-	97.8

### III- Synthesis of [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-1,5,9-Nonane triol [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-(**12**)

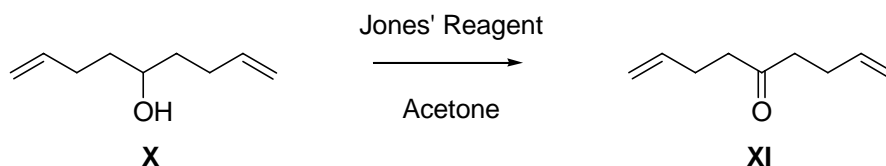


#### Nona-1,8-dien-5-ol<sup>8</sup> (**X**)

But-3-enyl magnesium bromide was generated from 4-bromobut-1-ene (2.5 g, 18.5 mmol) and magnesium (675 mg, 28 mmol) in diethyl ether (50 mL) and the mixture then cooled to -40°C (CO<sub>2</sub> / CH<sub>3</sub>CN). A solution of ethyl formate (685 mg, 9.3 mmol) in ether (5 mL) was added dropwise over 5 min. The reaction was allowed to warm to room temperature over 2 hours and then poured onto saturated ice cold ammonium chloride

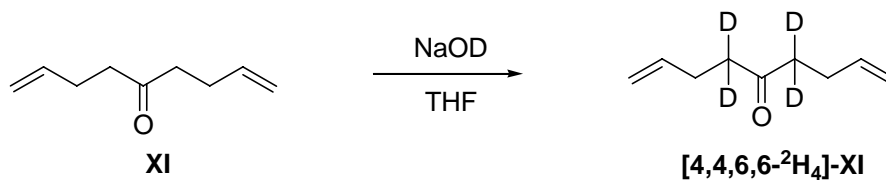
solution. The mixture was extracted with ether (3 x 30 mL), and the combined organic extracts washed with brine (15 mL), dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The crude product was refluxed in aqueous KOH (15 mL, 15%) for 3 hours to hydrolyse any formate ester, the reaction cooled, and extracted into ether and concentrated. The crude oil was purified by flash chromatography (EtOAc:Hex, 1:10) to give **X** (0.84 g, 65%) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.56-1.62 (m, 4H), 2.12-2.24 (m, 4H), 3.67 (tdd, 1H,  $J = 12.3, 7.7, 4.6$ ), 4.98 (ddt, 2H,  $J = 10.2, 2.3, 1.3$  Hz), 5.05 (ddt, 2H,  $J = 17.2, 3.5, 1.8$  Hz), 5.86 (ddt, 2H,  $J = 17.0, 10.2, 6.7$  Hz). GC/MS EI  $m/z$ (%) 140 ( $\text{M}^+$ , 0.05), 121 (0.8), 107 (10.3), 93 (13.4), 79 (55.2), 67 (43.2), 54 (42.1), 41 (100).

### Nona-1,8-dien-5-one (**XI**)<sup>8</sup>



To a solution of alcohol **X** (0.8 g, 5.7 mmol) in acetone (20 mL) at 0 °C was added sufficient Jones' reagent (~ 2 mL) dropwise that left a persistent yellow tint after 30 min. The reaction was checked by TLC then extracted into hexane (3 x 30 mL), dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc:Hex, 1:20) to give ketone **XI** (0.71 g, 90%) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.32 (q, 4H,  $J = 6.7$  Hz), 2.50 (t, 4H,  $J = 7.3$  Hz), 4.94-5.05 (m br, 4H), 5.79 (ddt, 2H,  $J = 17.3, 10.7, 6.5$  Hz). GC/MS EI  $m/z$ (%) 138 ( $\text{M}^+$ , 1.4), 123 (2.6), 109 (2.3), 96 (6.4), 83 (82.4), 67 (3.9), 55 (100), 39 (64.4).

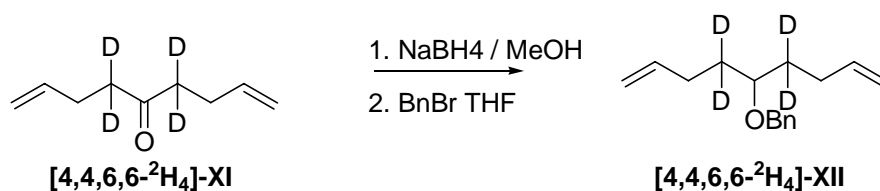
### [4,4,6,6- $^2\text{H}_4$ ]-Nona-1,8-dien-5-one, [4,4,6,6- $^2\text{H}_4$ ]-(**XI**)



Small portions of sodium (200 mg) were added to a stirred solution of  $\text{D}_2\text{O}$  (15 mL) at 0°C over 5 min. The solution of NaOD (~0.6 M) was allowed to warm to room

temperature and the ketone **XI** in THF (2 mL) was added and the reaction stirred vigorously for 36 hours. The mixture was extracted into hexane (2 x 40 mL), and the combined organic extracts washed with brine (15 mL), dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified on silica as for **20** to give **[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-XI** a colorless oil (860 mg, 79%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.26 (br d, 4H, *J* = 6.4 Hz), 2.42 (m, 8.3%<sup>1</sup>H), 4.91 (ddt, 2H, *J* = 10.1, 2.4, 1.2 Hz), 4.96 (ddt, 2H, *J* = 17.2, 3.5, 1.8 Hz), 5.74 (ddt, 2H, *J* = 17.2, 10.2, 6.6 Hz). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>) δ 27.5, 41.0 (quintet, CD<sub>2</sub>, *J* = 19.3 Hz) & 41.5 (t, CD, *J* = 19.2 Hz), 115.1, 137.0, 209.3-209.4 (m). GC/MS EI *m/z*(%) 142 (M<sup>+</sup>, 0.4), 126 (0.5), 100 (1.2), 85 (34.7), 57 (100), 39 (18.7).

**[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-Nona-1,8-dien-5-yloxy)methylbenzene[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-**(XII)****



To a solution of deuterated ketone **[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-XI** (600 mg, 4.2 mmol) in methanol (10 mL) at 0°C was added NaBH<sub>4</sub> (250 mg, 6.6 mmol) in one portion and the reaction stirred for 1 hour. The reaction was monitored by TLC and upon completion poured onto HCl (30 mL, 3M) and crushed ice (30 g). The mixture was extracted into ether (3 x 30 mL), the combined organic extracts washed with brine (15 mL), dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. GCMS analysis revealed the expected tetradeuterated alcohol.

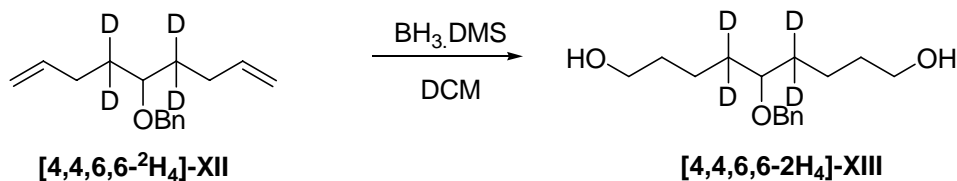
**[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-Nona-1,8-dien-5-ol** : GC/MS EI *m/z*(%) 143 (M<sup>+</sup>-1, 0.06), 129 (0.07), 114 (1.3), 110 (6.0), 96 (9.0), 87 (24.9), 84 (24.6), 83 (23.3), 82 (24.4), 69 (66.1), 59 (32.6), 58 (40.4), 57 (50.7), 43 (100), 30 (66.5).

The crude alcohol (500mg, 3.5 mmol) was then dissolved in THF (10 mL) and added to a suspension of NaH (200 mg, 5.2 mmol, 60% dispersion) in THF (10 mL) at -10°C dropwise over 5 min. The reaction was allowed to warm to room temperature over 1 hour and then cooled to -10 °C at which time benzyl bromide (0.45 mL, 3.8 mmol) was added dropwise followed by tetra-*n*-butyl ammonium iodide (65 mg, 0.17 mmol). The reaction

was allowed to warm up to room temperature overnight and poured onto ice the following morning. The mixture was extracted into ether (3 x 25 mL), the combined organic extracts washed with brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with EtOAc:Hex (1:20) to give the title compound as a colorless oil (350 mg, 43 % 2 steps).

**[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-Nona-1,8-dien-5-yloxy)methyl)benzene XII:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.11 (m, 4H), 3.40 (s, 1H), 4.48 (s, 2H), 4.93 (ddt, 2H, *J* = 1.2, 3.2, 10.3 Hz), 4.99 (ddt, 2H, *J* = 17.0, 3.5, 1.8 Hz), 5.80 (ddt, 2H, *J* = 17.0, 10.3, 6.7 Hz) 7.23-7.35 (m, 5H). <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>) δ 29.3 (2C), 30.5 (2C, br), 70.8, 77.5, 114.4 (2C), 127.4, 127.7, 128.2, 138.6 (2C), 138.8. GC/MS EI *m/z*(%) 234 (M<sup>+</sup>, 0.11), 219 (0.46), 191 (3.0), 177 (5.5), 159 (4.2), 148 (1.9), 131 (2.7), 118 (1.9), 107 (9.7), 91 (100), 85 (4.8), 65 (17.0), 57 (10.6).

**[4,4,6,6-<sup>2</sup>H<sub>4</sub>]-5-(Benzyloxy)nonane-1,9-diol, [4,4,6,6-<sup>2</sup>H<sub>4</sub>]-XIII**



BH<sub>3</sub>.DMS (0.63 mL, 3.2 mmol, 5M in diethyl ether) was added to a solution of diene **XII** (350 mg, 1.5 mmol) in DCM (20 mL) under nitrogen at -10°C. The reaction was allowed to warm to room temperature over 2 hours and then ethanol (5 mL) was added very cautiously dropwise. After the reaction subsided, sodium hydroxide (20 mL, 5M) was added followed by hydrogen peroxide (20 mL, 30%). The reaction was left to stir at RT for 10 hours, then extracted with DCM (3 x 50 mL) and the combined organic extracts washed with brine and concentrated *in vacuo*. The odiferous residue was purified by flash chromatography eluting with EtOAc:Hexane, (1:1) which afforded **XIII** as a viscous oil (120 mg, 30%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.42 (m, 4H, *J* = 7.92 Hz), 1.56 (m, 4H, *J* = 7.92 Hz), 3.4 (s br, 1H), 3.62 (t, 4H, *J* = 6.5 Hz), 4.51 (s, 2H), 7.10-7.35 (m, 5H). <sup>13</sup>C



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<sup>8</sup> Nagai, M.; Lazor, J.; Wilcox, C. S. *J. Org. Chem.* **1990** 55 (11) 3440-3442.