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Synthesis of Deuterated C-6 and C-9 Flavour Volatiles.

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SUMMARY

Regiospecific deuterogenation of alkynols and chain extension of deuterated C-6 alkyl halides by alkylation with malondialdehyde derivatives was used to synthesise a series of deuterated C-6 and C-9 flavour volatiles. Reduction of 3-hexyn-1-ol with deuterium gas using Wilkinson's catalyst required protection of the alcohol as the *tert*-butyldimethylsilyl ether to speed reaction and minimise scrambling of deuterium. Deuterogenation of 5-hexyn-1-ol proceeded cleanly without protection to give 5,5,6,6-$^2H_4$-hexanol which was converted to 5,5,6,6-$^2H_4$-hexyl bromide and the corresponding Grignard reagent. Reaction of this Grignard reagent with 3-trimethylsiloxy-2-propenal gave 8,8,9,9-$^2H_4$-2*E*-nonenal. Deuterogenation of 3-hexyn-1-ol with Lindlar catalyst gave 3,4-$^2H_2$-3*Z*-hexenol which was converted to the corresponding iodide and used to synthesise 6,7-$^2H_2$-2*E*,6*Z*-nonadienal and 6,7-$^2H_2$-2*E*,6*Z*-nonadienol. Wilkinson reduction of the *tert*-butyldimethylsilyl derivative of 3-nonyn-1-ol was used to synthesize 3,3,4,4-$^2H_4$-nonanol and 3,3,4,4-$^2H_4$-nonanal.

Key Words: nonanal, 2*E*-nonenal, 2*E*,6*Z*-nonadienal, 2*E*,6*Z*-nonadienol, flavour volatiles, deuterium.

INTRODUCTION

Nonanal, 2*E*-nonenal and 2*E*,6*Z*-nonadienal are potent flavour and aroma compounds (odour threshold values 1, 0.08 and 0.01 ppb respectively in water[1]) formed by cleavage of fatty acid hydroperoxides in a wide variety of foods and plant and animal tissues. Nonanal and 2*E*-nonenal both possess strong fatty, floral odours.[1,2] 2*E*-Nonenal is a key contributor to the flavour of fruit[3], coffee[4], toasted bread[5] and oxidative off-flavours in high fat foods.[6,7] 2*E*,6*Z*-Nonadienal has a

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distinctive cucumber-like odour and also occurs widely in fruit, vegetables, oils and high fat foods.[6,8] These C-9 aldehydes not only contribute to the flavour of a wide variety of food products but their concentrations may also serve as indicators of lipid autoxidation and of sample abuse. Quantitation of these volatile flavour compounds at part per billion levels in foods requires the synthesis of regiospecifically deuterated derivatives for use as internal standards in isotope dilution assays.

We recently reported[9] a synthesis of deuterated 2*E*-hexenal by reaction of 3-trimethylsiloxy-2-propenal, generated *in situ* from the potassium salt of malondialdehyde **4** (**Scheme I**), with 3,3,3-$^{2}H_3$-propyl bromide. This procedure should provide a general route to deuterated 2*E*-enals given the requisite deuterated alkyl halides. We now report the extension of this methodology to provide deuterated nonenals and also the synthesis of the requisite deuterated alkyl halides by regiospecific deuterogenation of alkynols.

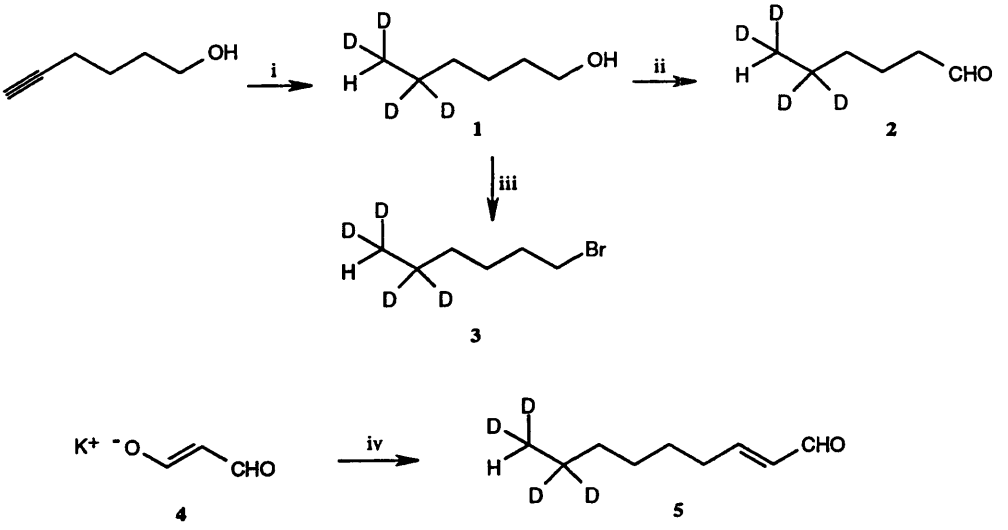
RESULTS AND DISCUSSION

Attempted deuterogenation of 3-hexyn-1-ol with Wilkinson's catalyst (RhCl $(PPh_3)_3$) proceeded slowly (48 hours) and in low yield (58%) to give an incompletely deuterated hexanol, found to be predominantly d_3 by mass spectral analysis. It was believed that complexation of the alcohol function with the rhodium might be slowing recycling of the catalyst and allowing alternative reaction pathways to proceed leading to scrambling of the label. The alcohol was therefore protected as the *tert*-butyldimethylsilyl ether. Deuterogenation proceeded more rapidly however mass spectral analysis of the molecular ion of the resulting hexyl silyl ether still showed significant under deuterogenation (29% d_3 by GCMS). A two step reduction of the hexynol silyl ether involving sequential deuterogenation with Lindlar's and then Wilkinson's catalysts gave no better results (34% d_3). Deuterogenation was then attempted using 5-hexyn-1-ol (**Scheme I**). In this case, reduction proceeded cleanly and rapidly without protection to afford 5,5,6,6-$^{2}H_4$-hexanol **1** in 90% yield. Regiospecific incorporation of four deuterium atoms was demonstrated by ^{1}H and ^{13}C nmr and later GCMS analysis. Oxidation of **1** with the Dess-Martins periodinane[10,11] gave 5,5,6,6-$^{2}H_4$-hexanal **2** in 83% yield.

Hexanol **1** was converted to the bromide **3** in 84 % yield using Br_2/PPh_3/imidazole. Conversion of bromide **3** to the corresponding Grignard reagent and reaction with 3-trimethylsiloxy-2-propenal, generated *in situ*[9] from the potassium salt of malondialdehyde **4**, gave pure samples of 8,8,9,9-$^{2}H_4$-2*E*-nonenal **5** in 42% yield. Use of the alternative reagent, 3-dimethylamino-2-propenal[12] gave lower yields. Regiospecific deuteration was demonstrated by ^{1}H and ^{13}C nmr spectroscopy while

GCMS showed the presence of ca. 2.5% of 8,8,9,9-$^2H_4$-2Z-nonenal. Mass spectral analysis of the $(M+NH_4)^+$ ion m/z 162 obtained using ammonia gas for chemical ionization during GCMS indicated the sample contained not more than 1% of the d_3 analogue. 2,3-$^2H_2$-2*E*-Nonenal has been prepared by pyridinium chlorochromate oxidation, then Lindlar reduction, of 2-nonynol which gave a 1:4 mixture of 2*E* and 2Z-nonenals which were subsequently separated by hplc.[6]

Scheme I

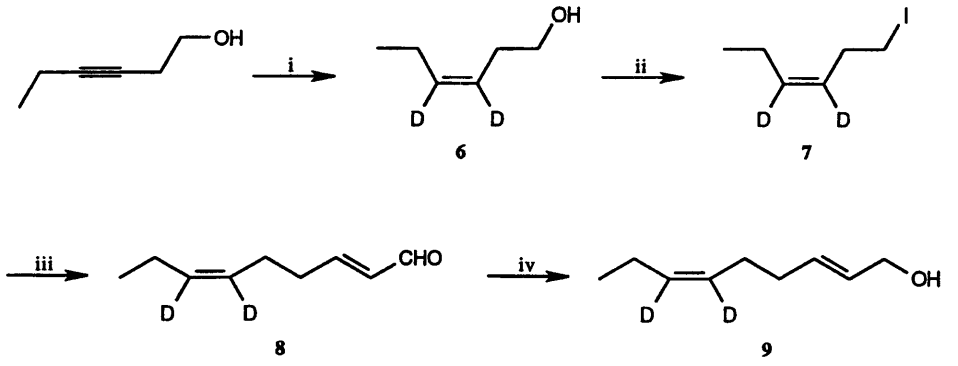


i) $Rh(PPh_3)_3Cl/D_2$, benzene, 90%. ii) Dess-Martin periodinane, CH_2Cl_2, 83%. iii) PPh_3/imidazole/Br_2, CH_2Cl_2, 84%. iv) Me_3SiCl/Et_3N/DMAP, Et_2O then 3/Mg, THF, 42%.

Partial deuterogenation of 3-hexyn-1-ol with Lindlar's catalyst[10] (**Scheme II**) gave 3,4-$^2H_2$-3Z-hexenol **6** (>96% d_2 by GCMS) which was converted to 3,4-$^2H_2$-3Z-hexenyl iodide **7** (78%) and coupled with 3-trimethylsiloxy-2-propenal, prepared *in situ* as above[9], to give 6,7-$^2H_2$-2*E*,6Z-nonadienal **8** (22%). Reduction of dienal **8** with $NaBH_4$ gave 6,7-$^2H_2$-2*E*,6Z-nonadienol **9** (89%) recently identified as responsible for a metallic off-flavour of sour cream buttermilk[13]. Dienal **8** has also been synthesised from 3,4-$^2H_2$-3Z-hexenyl chloride and 3-(*N*-methylanilino)-2-propenal with purification by hplc.[6]

Finally deuterated nonanal **12** was synthesised by reduction of the *tert*-butyldimethylsilylated derivative of 3-nonyn-1-ol **10b** with deuterium gas and Wilkinson's catalyst (**Scheme III**). In this

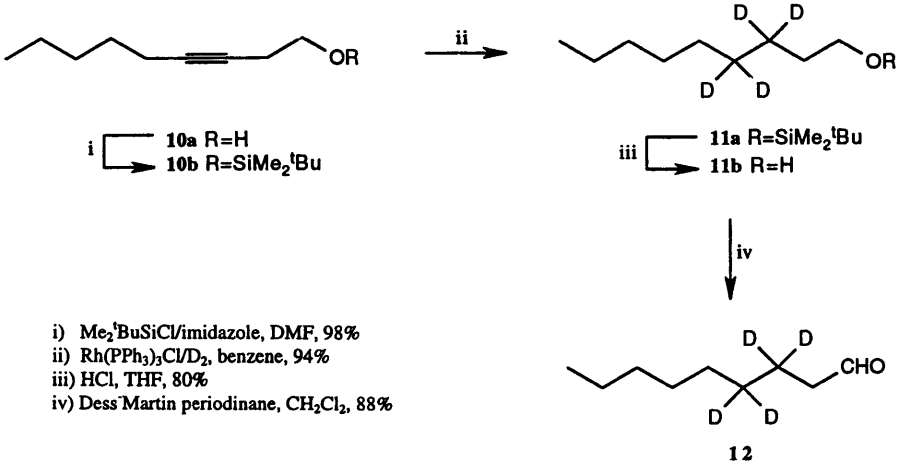
Scheme II



i) Lindlar's catalyst/quinoline/D_2, pentane, 86%[10]. ii) PPh_3/imidazole/I_2, CH_2Cl_2, 78%. iii) 4/Me_3SiCl/Et_3N/DMAP, Et_2O then 7/Mg, THF, 22%. iv) $NaBH_4$, MeOH, 89%.

case, reduction proceeded smoothly to give the d_4-silyl ether **11a** (94%). Analysis of the fragment ions in the mass spectrum corresponding to M^+- Me and M^+-*t*Bu (m/z 247 and 205 respectively) showed this material contained not more than 2% of the d_3 isomer. Acid hydrolysis of **11a** gave deuterated nonanol **11b** in 80% yield . Oxidation of **11b** with the Dess-Martins periodinane[10,11] then gave 3,3,4,4-$^2H_4$-nonanal **12** in 88% yield. A non-aqueous workup of the periodinane oxidation reaction (see experimental) was essential to prevent trimerization of **12**.

Scheme III



i) $Me_2{}^tBuSiCl$/imidazole, DMF, 98%
ii) $Rh(PPh_3)_3Cl/D_2$, benzene, 94%
iii) HCl, THF, 80%
iv) Dess Martin periodinane, CH_2Cl_2, 88%

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Reaction of deuterated Grignard reagents with malondialdehyde equivalents provides a general route to deuterated 2*E*-enals. The required deuterated alkylating agents can be prepared by selective deuterogenation of acetylenic alcohols if suitable regioisomers or protecting groups are used. Deuterated nonanal, 2*E*-nonenal and 2*E*,6*Z*-nonadienal prepared by this procedure have been used in stable isotope dilution assays to measure low ppb levels of these compound in dairy products.

EXPERIMENTAL

NMR spectra were recorded on a Joel GX270 (270MHz) spectrometer in $CDCl_3$ and referenced to chloroform at δ 7.27 and 77.0 for ^1H and ^{13}C spectra respectively. ^{13}C NMR spectra were assigned by direct comparison with unlabelled compounds.[14] GCMS was carried out using an HP 5890 Series II gas chromatograph fitted with a 30m x 0.25 mm ID Carbowax column, 0.25μm film thickness; temperature program 40° C, hold 5 min, then 5° C/min to 240 °C, 2 psi He head pressure directly coupled to a VG70-250S mass spectrometer (VG Instruments, Manchester, UK) with an ionization energy of 70eV (EI) or 40 eV (CI). All reagents (Aldrich Chemical Company) were used without further purification unless stated. Ether is diethyl ether. Dry ether and dry THF were freshly distilled from sodium-benzophenone under N_2. Room temperature (RT) is 18-23° C. Flash column chromatography was carried out using 40 μm (flash) silica gel (Alltech Associates Inc.) with freshly distilled solvents as described. Short path distillation was carried out using a GKR-51 Kugelrohr (Büchi, Switzerland).

5,5,6,6-$^2H_4$-Hexan-1-ol (1)

Freshly prepared tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst[15]), (0.10 g, 0.11 mmol) was added at RT to a solution of 5-hexyn-1-ol (0.50 g, 5.09 mmol) in benzene (20 ml). An hydrogenation apparatus similar to that described by Vogel[16] was used. The reaction flask was swept with D_2 gas (~10 ml, 99.8% atom D) and the contents were stirred vigorously while the uptake of D_2 was monitored. After 1.5 hrs, 245 ml of D_2 (10.2 mmol) had been consumed and uptake ceased. The reaction mixture was filtered through a short plug of celite and rinsed with ether (2 x 20 ml). The solvent was removed *in vacuo* and the product was purified by short path distillation to give **1** (0.49 g, 90%) as a colourless oil, bp 155-160 °C/760 mmHg; ^1H NMR δ 3.59 (2H, t, J = 7.0Hz, CH_2OH), 2.31 (1H, bs, **OH**), 1.53 (2H, quint, J = 7.0 Hz, CH_2CH_2OH), 1.38-1.26 (4H, m, $CD_2CH_2CH_2$), 0.82 (1H, bs, HD_2C); ^{13}C NMR δ 62.8 (C-1), 32.7 (C-2), 31.4 (C-4), 25.4 (C-3), 21.7 (quintet, C-5), 13.2 (quintet, C-6); EIMS (m/z, rel. int.): 88 (M^+-H_2O, 17), 87 (1.8), 73 (16), 72 (16), 71 (19), 60 (100), 59 (64), 55 (44), 43 (61), 29 (64).

5,5,6,6-$^2H_4$-Hexanal (2)

A solution of **1** (0.268 g, 2.52 mmol) in CH_2Cl_2 (1.0 ml) was added to a stirred slurry of freshly prepared Dess-Martin periodinane[11] (1.29 g, 3.03 mmol) in CH_2Cl_2 (25 ml) at 0° C under N_2 . The reaction mixture was warmed to RT, stirred for 3 hrs then diluted with pentane (25 ml) and passed through a short plug of silica under reduced pressure and rinsed with pentane/CH_2Cl_2 (1:1, 40 ml). The solvent was removed *in vacuo* and the crude product was purified by short path distillation to give **2** (0.218 g, 83%) as a colourless, mobile oil, bp 130-135 °C/760 mmHg; ^{1}H NMR δ 9.72 (1H, t, J = 2.0 Hz, CHO), 2.38 (2H, dt, J = 7.3, 2.0 Hz, CH_2CHO), 1.64-1.53 (2H, m, CH_2CH_2CHO), 1.24 (2H, bt, J = 8.0 Hz, CD_2CH_2), 0.87 (1H, bs, HD_2C); ^{13}C NMR δ 202.5 (C-1), 43.8 (C-2), 31.0 (C-4), 21.7 (C-3), 13.0 (quintet, C-6), C-5 not observed; EIMS (m/z, rel. int.): 104 (0.3), 103 (0.2), 86 (6), 85 (3), 76 (14), 60 (40), 59 (43), 44 (100).

1-Bromo-5,5,6,6-$^2H_4$-hexane (3)

A solution of bromine (1.29 g, 8.06 mmol) in CH_2Cl_2 (2 ml) was added to a vigorously stirred solution of imidazole (0.69 g, 10.1 mmol) and triphenylphosphine (2.11 g, 8.06 mmol) in CH_2Cl_2 (20 ml) at 0° C. After 5 min, a solution of **1** (0.713 g, 6.72 mmol) in CH_2Cl_2 (5 ml) was added dropwise and the reaction mixture allowed to warm to RT over 30 min. The solvent was removed under reduced pressure and the residue was triturated with pentane-ether (10:1, 20 ml) in the presence of a small quantity (~1 g) of silica gel. The supernatant was filtered through a short plug of silica and concentrated *in vacuo* to give a crude oil that was purified by short path distillation to give **3** (0.95g, 84%) as a colourless oil, bp 70-75 °C/35 mmHg; ^{1}H NMR δ 3.42 (2H, t, J = 7.0 Hz, CH_2Br), 1.87 (2H, quint, J = 7.0 Hz, CH_2CH_2Br), 1.47-1.38 (2H, m, $CH_2CH_2CH_2$Br), 1.28 (2H, bt, J = 7.0 Hz, CD_2CH_2), 0.85 (1H, bs, HD_2C); ^{13}C NMR δ 34.1 (C-1), 32.9 (C-2), 30.8 (C-4), 27.9 (C-3), C-5, 6 not observed.

8,8,9,9-$^2H_4$-2*E*-Nonenal (5)

Freshly distilled trimethylsilyl chloride (0.61 g, 5.6 mmol) was added to a slurry of potassium malondialdehyde **4**[17] (0.62 g, 5.6 mmol) and *N,N*-dimethylaminopyridine (34 mg, 0.3 mmol) in dry ether (10 ml) and triethylamine (57 mg, 0.6 mmol) at RT. The reaction was stirred continuously for 24 hrs under an atmosphere of dry N_2 to give an ethereal solution of 3-trimethylsiloxy-2-propenal.[9,18] 5,5,6,6-$^2H_4$-hexyl magnesium bromide (5.6 mmol) [prepared by the addition of **3** (0.94 g, 5.6 mmol) to a vigorously stirred suspension of magnesium turnings (0.15 g, 6.1 mmol) and

iodine (~5 mg, catalytic) in dry THF (4.0 ml) under N_2 at a rate sufficient to maintain gentle reflux] was added to an ethereal solution of 3-trimethylsiloxy-2-propenal at -78° C prepared as described above. The reaction was warmed to RT over 30 min and quenched by the addition of dilute HCl (10% v/v, 10 ml) and extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with water (30 ml), sat. brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to gave an oil that was purified by flash chromatography on silica gel eluting with hexane-ether (20:1) to yield **5** (0.34 g, 42%)[2] as a colourless oil; ^{1}H NMR δ 9.51 (1H, d, J = 7.9Hz, CHO), 6.86 (1H, dt, J = 15.6, 6.7Hz, CH=CHCHO), 6.12 (1H, dd, J = 15.6, 7.9Hz, =CHCHO), 2.34 (2H, q, J = 6.7Hz, CH_2CH=), 1.52 (2H, m, CH_2CH_2CH=), 1.46-1.28 (4H, m, $CD_2CH_2CH_2$), 0.84 (1H, bs, HD_2C); ^{13}C NMR δ 193.9 (C-1), 158.9 (C-3), 132.8 (C-2), 32.8 (C-4), 31.4 (C-7), 28.9 (C-5), 27.9 (C-6), C-8, 9 not observed; EIMS (m/z, rel. int.) 126 (3), 125 (3), 112 (6), 100 (30), 88 (25), 83 (81), 70 (100), 57 (78), 41 (76); CIMS (NH_3): 162 $(M+NH_4)^+$.

1-Iodo-3,4-$^2H_2$-3*Z*-hexene (7)

Iodine (2.52 g, 9.94 mmol) was added to a vigorously stirred solution of imidazole (0.846 g, 12.4 mmol) and triphenylphosphine (2.82 g, 10.7 mmol) in CH_2Cl_2 (50 ml) at 0° C. After 5 min, a solution of **6**[10] (0.846 g, 8.3 mmol) in CH_2Cl_2 (5 ml) was added dropwise and the reaction mixture allowed to warm to RT over 30 min. The solvent was removed under reduced pressure and the residue was triturated in the presence of a small quantity (~1 g) of silica gel with pentane-ether (10:1, 20 ml). The supernatant was filtered through a short plug of silca and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane to yield iodide **7** (1.37 g, 78%) as a colourless, mobile liquid that rapidly discoloured on exposure to light; ^{1}H NMR δ 3.13 (2H, t, J = 7.3 Hz, CH_2I), 2.62 (2H, t, J = 7.3 Hz, CH_2CH_2I), 2.04 (2H, q, J = 7.5 Hz, CH_3CH_2), 0.98 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR δ 133.7 (t, C-4), 126.7 (t, C-3), 31.3 (C-2), 20.6 (C-5), 14.1 (C-6), 5.5 (C-1); EIMS (m/z, rel. int.) 212 (M^+, 1), 155 (3), 141 (2), 127 (6), 85 (100), 56 (39), 42 (32); EIMS (m/z, rel. int.): 212 (M^+, 0.8), 155 (5), 141 (3), 127 (11), 85 (100), 57 (86), 42 (86).

6,7-$^2H_2$-2*E*, 6*Z*-Nonadienal (8)

A solution of 3,4-$^2H_2$-3*Z*-hexenyl magnesium iodide (9.08 mmol) [prepared from **7** (1.93 g, 9.08 mmol) and magnesium turnings (0.243 g, 9.98 mmol) as described above] was added at -78° C to an ethereal solution of 3-trimethylsiloxy-2-propenal (9.08 mmol) prepared as above. The reaction was warmed to RT over 30 min and quenched by the addition of dilute HCl (10% v/v, 10 ml) and

extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with water (30 ml), sat. brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to gave an oil that was purified by flash chromatography on silica gel eluting with hexane-ether (20:1) to yield **8** (0.28 g, 22%) as a colourless oil; ^{1}H NMR δ 9.50 (1H, d, J=7.8 Hz, CHO), 6.84 (1H, dt, J = 15.6, 6.7 Hz, CH=CHCHO), 6.13 (1H, dd, J = 15.6, 7.8 Hz, CHCHO), 2.40 (2H, m, CH_2CH=), 2.26 (2H, m, =CDCH_2), 2.04 (2H, q, J = 7.5 Hz, CH_2CH_3), 0.97 (3H, t, J = 7.5Hz, CH_3); ^{13}C NMR δ 194.0 (C-1), 158.0 (C-3), 133.2 (C-2), 132.8 (t, C-7), 126.3 (t, C-6), 32.7 (C-4), 25.3 (C-5), 20.5 (C-8), 14.2 (C-9); EIMS (m/z, rel. int.): 140 (M^+, 0.8), 125 (1), 122 (0.5), 111 (4), 96 (6), 83 (5) 81 (8), 71 (87), 70 (100), 42 (81); CIMS (NH_3) 158 $(M+NH_4)^+$, 141 $(M+H)^+$.

6,7-$^2H_2$-2*E*, 6*Z*-Nonadien-1-ol (9)

A solution of **8** (87 mg, 0.62 mmol) in ether (1 ml) was added to a solution of sodium borohydride (0.1 g) in methanol (5 ml) at 0° C under N_2. The reaction mixture was stirred for 30 min and warmed to RT, quenched with sat. NH_4Cl (2 ml) and extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with water (20 ml), sat. brine (20 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude product that was purified by flash chromatography on silica gel eluting with hexane-ether (2:1) to yield **9** (78 mg, 89%)[13] as a colourless oil; ^{1}H NMR δ 5.68 (2H, m, CH=C**H**CH_2OH), 4.08 (2H, d, J = 4.3 Hz, CH_2OH), 2.11 (4H, bs, CH_2CH_2), 2.03 (2H, q, J = 7.5 Hz, CH_2CH_3), 1.60 (1H, bs, OH), 0.95 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR δ 132.6 (C-2), 131.2 (t, C-7), 129.2 (C-3), 128.2 (t, C-6), 63.6 (C-1), 32.2 (C-4), 26.5 (C-5), 20.3 (C-8), 14.2 (C-9); EIMS (m/z, rel. int.) 124 (M^+-H_2O), 8), 111 (16), 109 (9), 96 (23), 80 (24), 71 (97), 54 (45), 43 (100); CIMS (NH_3) 160 $(M+NH_4)^+$, 142 $(M+NH_4-H_2O)^+$.

1-*tert*-Butyldimethylsiloxynon-3-yne (10b)

3-Nonyn-1-ol (2.57 g, 18.3 mmol) was added dropwise to a solution of *tert*-butyldimethylsilyl-chloride (3.31 g, 21.9 mmol) and imidazole (3.11 g, 45.7 mmol) in DMF (7.0 ml) at 0° C under N_2. The reaction mixture was warmed to RT, stirred for 1 hr, diluted with water (30 ml) and extracted with ether (3 x 40 ml). The combined ethereal extracts were washed with water (50 ml), sat. brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **10b** as a colourless oil (4.57 g, 98%); ^{1}H NMR δ 3.7 (2H, t, J = 7.0 Hz, CH_2O), 2.37 (2H, tt, J = 7.3, 2.4 Hz, $CH_2C\equiv$), 2.14 (2H, tt, J = 7.0, 2.4 Hz, $CH_2C\equiv$), 1.55-1.40 (2H, m, $CH_2CH_2C\equiv$), 1.40-1.25 (4H, m, $CH_3CH_2CH_2$), 0.93-0.87 (12H, m, CH_3, $(CH_3)_3C$), 0.08 (6H, s, $(CH_3)_2Si$); ^{13}C NMR δ 81.5 (C-3), 76.8 (C-4), 62.4 (C-1), 31.2 (C-7), 28.8 (C-6), 26.9 ($(CH_3)_3C$), 23.3 (C-2), 22.3 (C-8), 18.8 (C-5), 18.5 ($(CH_3)_3C$), 14.1

(C-9), -5.1 ($CH_3)_2Si$). EIMS (m/z, rel. int.): 239 (M^+-Me, 0.3), 197 (30), 141 (13), 121 (48), 89 (37) 75 (100), 73 (55).

1-*tert*-Butyldimethylsiloxy-3,3,4,4-$^2H_4$-nonane (11a)

Freshly prepared *tris*(triphenylphosphine)rhodium(I) chloride[13] (0.10 g, 0.11 mmol) was added at RT to a solution of **10b** (1.0 g, 3.93 mmol) in benzene (20 ml). The reaction flask was swept with D_2 gas (~10 ml, 99.8% atom D) and the contents was stirred vigorously while the uptake of D_2 was monitored. After 18 hrs, 180 ml of D_2 (7.5 mmol) had been consumed and uptake ceased. The reaction mixture was diluted with hexane (20 ml), filtered through a short plug of silica and rinsed with hexane-ether (20:1) (2 x 20 ml). The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with hexane-ether (20:1) to yield **11a** (0.97g, 94%) as a colourless oil; ^{1}H NMR δ 3.61 (2H, t, J = 6.6 Hz, CH_2O), 1.50 (2H, t, J = 6.6 Hz, CH_2CH_2O), 1.27 (8H, bs, $(CH_2)_4$), 0.93-0.87 (12H, m, CH_3, $(CH_3)_3C$), 0.06 (6H, s, $(CH_3)_2Si$); ^{13}C NMR δ 63.3 (C-1), 32.7 (C-2), 32.0 (C-7), 29.5, 29.4, (C-5,6), 26.1 ($(CH_3)_3C$-), 22.8 (C-8),18.5 ($(CH_3)_3C$), 14.2 (C-9), -5.1 ($(CH_3)_2Si$), C-3, 4 not observed; EIMS (m/z, rel. int.): 247 (M^+-Me, 1), 205 (100), 89 (9), 75 (62).

3,3,4,4-$^2H_4$-Nonan-1-ol (11b)

Dilute HCl (10% v/v, 10 ml) was added to a solution of **11a** (0.97 g, 3.8 mmol) in THF (20 ml) at RT and stirred until the reaction mixture was homogeneous (1 hr). The solution was extracted with CH_2Cl_2 (3 x 20 ml) and the combined extracts were washed with sat. $NaHCO_3$ (30 ml) and sat. brine (30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude product which was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (3:1) and then by short path distillation to yield **11b** (0.45 g, 80%) as a colourless oil, bp 105-110 °C/20 mmHg; ^{1}H NMR δ 3.64 (2H, t, J = 6.6 Hz, CH_2OH), 1.55 (2H, t, J = 6.6 Hz, CH_2CH_2OH), 1.32 (1H, bs, OH), 1.27 (8H, bs, $(CH_2)_4$), 0.89 (3H, t, J = 6.8Hz, CH_3); ^{13}C NMR δ 63.1 (C-1), 32.6 (C-2), 32.0 (C-7), 29.4, 29.3 (C-5,6), 22.8 (C-8), 14.2 (C-9), C-3,4 not observed; EIMS (m/z, rel. int.): 130 (M^+-H_2O, 2), 129 (3), 101 (36), 100 (29), 87 (32), 86 (44), 72 (78), 57 (100), 43 (80); CIMS (isobutane) 131 $(M+H-H_2O)^+$.

3,3,4,4-$^2H_4$-Nonanal (12)

A solution of **11b** (48 mg, 0.32 mmol) in CH_2Cl_2 (0.5 ml) was added to a stirred slurry of freshly prepared Dess-Martin periodinane[11] (0.17 g, 0.39 mmol) in CH_2Cl_2 (10 ml) at 0° C under N_2. The reaction mixture was warmed to RT and stirred for 15 min then diluted with hexane (10 ml) and

passed through a short plug of silica under reduced pressure and rinsed with hexane/CH_2Cl_2 (1:1, 20 ml). The solvent was removed *in vacuo* and the crude product purified by short path distillation to give **12** (42 mg, 88%) as a colourless, mobile oil, bp 100-110 °C/25 mmHg; ^{1}H NMR δ 9.76 (1H, t, J = 2.0 Hz, CHO), 2.40 (2H, m, CH_2CHO), 1.27 (8H, bs, $(CH_2)_4$), 0.88 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR δ 202.7 (C-1), 43.7 (C-2), 31.8 (C-7), 29.1 (C-5 and C-6), 22.7 (C-8), 14.1 (C-9), C-3, 4 not observed; EIMS (m/z, rel. int.): 146 (M^+, 0.4), 145 (M^+-H, 0.2), 128 (2.3), 127 (2.8), 126 (2.0), 116 (13), 102 (34), 99 (26), 84 (25), 70 (39), 59 (100), 43 (82). CIMS (NH_3): 147 ($M+H^+$), 146 ($M+NH_4^+-H_2O$).

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