The Synthesis of 3,4-$^2H_2$-3Z-Hexenal and 6,6,6-$^2H_3$-3Z-Hexenal.

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Summary

6,6,6-$^2H_3$-3Z-Hexenal (3b) has been prepared in 89% yield and in greater than 94% purity by the oxidation of 6,6,6-$^2H_3$-3Z-Hexen-1-ol (2b) with the Dess/Martin periodinane (1) in fluorotrichloromethane (freon 11). Use of the freon solvent greatly improved the recovery of this volatile aldehyde. Similarly the oxidation of 3,4-$^2H_2$-3Z-hexen-1-ol (5) yielded 3,4-$^2H_2$-3Z-hexenal (6) in a 92% isolated yield with a purity of greater than 99%. 3,4-$^2H_2$-3Z-Hexen-1-ol (5) was prepared in 87% by the catalytic deuterogenation of 3-hexyn-1-ol (4) in an improved synthetic procedure.

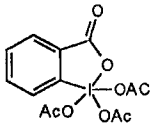
Key Words 6,6,6-$^2H_3$-3Z-hexenal, 3,4-$^2H_2$-3Z-hexenal, 3Z-hexenal, synthesis, deuterium.

Introduction

3Z-Hexenal (3a) occurs widely and is formed by the enzymatic and oxidative degradation of unsaturated lipid material[1,2,3]. 3Z-Hexenal is a key impact aroma compound found in many fruit[4], vegetables[5] and leaves[6] and its presence in processed fatty foods[1,7,8] has been associated with taints and undesirable off-flavours[9]. Release of 3Z-hexenal from disrupted plant tissue inhibits pollen germination[10] while mixtures of volatiles containing 3Z-hexenal show semiochemical properties[11]. We required a practical synthesis of deuterium labelled 3Z-hexenal for use in the study of aroma biosynthesis.

Results and Discussion

3,4-$^2H_2$-3Z-Hexenal (6) has been prepared by the pyridinium dichromate (PDC) oxidation of 3,4-$^2H_2$-3Z-hexen-1-ol (5)[6]. However attempts to oxidise 6,6,6-$^2H_3$-3Z-Hexen-1-ol (2b)[12] under these conditions failed. Other reagents, including DMSO-oxalyl chloride[13], pyridinium chlorochromate[14], Jones' Reagent[15] and dichlorotris(triphenylphosphine)ruthenium(II)[16] were also unsuccessful. Over-oxidation to the acid, concomitant bond migration to the conjugated 2-ene system, dehydration and cyclization were all observed by GCMS and mass recoveries were always poor. Surprisingly the Dess/Martin (D/M) periodinane (1), prepared by the authors' original procedure[17] was also found to be ineffective in achieving this apparently simple transformation. However a recent modification to the original



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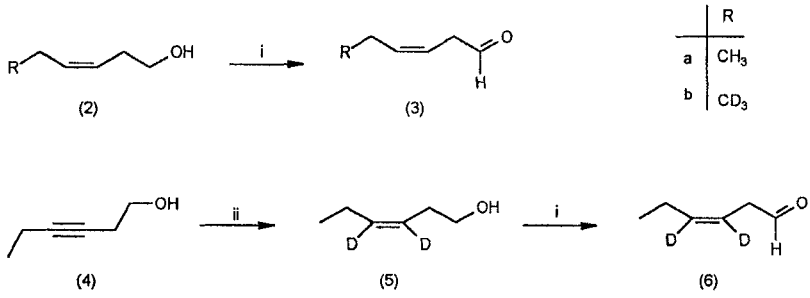
preparation of (1)[18] prompted us to reinvestigate the use of this reagent in the synthesis of deuterium labelled 3Z-hexenal (Scheme 1).

3Z-hexen-1-ol (2a) was added to a slurry of periodinane (1)[18] in dichloromethane and the reaction was monitored by GC. After stirring at room temperature for 3 hours, (2a) was no longer present and a single, more volatile component was the only detectable product. On isolation, this material gave NMR and MS data consistent with 3Z-hexenal (3a). However the complete removal of dichloromethane (as judged by ^{1}H NMR) resulted in considerable losses of product. Recoveries were as low as 40%[19] when small quantities of (3a), typically 100mg or less, were handled.

An alternative solvent with greater volatility than dichloromethane was needed for ease of removal. Fluorotrichloromethane (Freon 11, bp 23.7°C) proved a useful substitute. In fluorotrichloromethane, 3Z-hexen-1-ol was converted cleanly to 3Z-hexenal by 1.5 equivalents of (1) over 18 hours at room temperature. After a conventional work up, the freon was removed at atmospheric pressure under a stream of dry nitrogen on a modified rotary evaporator[20] to give 3Z-hexenal (3a) in an 89% yield with a purity of 96% by GC. Physical data was identical to that of 3Z-hexenal prepared in dichloromethane and no fluorotrichloromethane was detected by ^{13}C NMR.

Scheme 1. **Synthesis of deuterated 3Z-Hexenals.**



i, (1) (1.5eq), $FCCl_3$, 18hrs., RT.

ii, D_2, Lindlar's Catalyst.

Under these conditions 6,6,6-$^2H_3$-3Z-hexen-1-ol (2b) was oxidised quantitatively to 6,6,6-$^2H_3$-3Z-hexenal (3b) and recovered in 89% yield with a purity of greater than 94% by GC. ^{1}H NMR revealed a characteristic aldehydic triplet at 9.65 ppm with an associated signal in the ^{13}C NMR spectrum at 199.2 ppm. GCMS gave a molecular ion of m/z=101. Decomposition was detected in samples stored under nitrogen at -20°C after one month, however decomposition was less in samples stored as solutions in pentane at -20°C.

Having established conditions to effect the oxidation of 6,6,6-$^2H_3$-3Z-hexen-1-ol (2b) to the corresponding aldehyde (3b) in high yield, we investigated a more direct synthesis of deuterium labelled 3Z-hexenal. 3-Hexyn-1-ol (4) is commercially available and is readily reduced to the corresponding *cis*-alkene by hydrogenation over Lindlar's catalyst. Under these conditions deuterium can be added stereospecifically to give a d_2-*cis*-alkene without scrambling of the label. Hydrogenation of (4) with D_2 in the presence of poisoned Lindlar catalyst afforded 3,4-$^2H_2$-3Z-hexen-1-ol (5) in 87% yield with 99% purity by GC. No alkenic protons were detectable by ^{1}H NMR,

while comparison with unlabelled 3Z-hexen-1-ol (2a) showed the five proton multiplet of the C2, C5 and OH signals had collapsed to a broad triplet (C2) and a second, less complex multiplet associated with the C5 and OH protons. Comparison of the ^{13}C NMR spectra showed the two alkenic singlets of (2a) had been replaced by a pair of 1:1:1 triplets. GCMS gave a molecular ion of *m/z*=102.

Oxidation of 3,4-$^2H_2$-3Z-hexen-1-ol (5) with (1) in fluorotrichloromethane gave 3,4-$^2H_2$-3Z-hexenal (6) in a 92% yield with a purity of 99% by GC. Comparisons between the ^1H and ^{13}C NMR spectra of (6) and unlabelled 3Z-hexenal (3a) were consistent with deuteration at C3 and C4. No alkenic resonances were detected in the proton spectrum, while the associated collapse in multiplicity for protons at C2 and C5 was observed. No alkenic signals were observed in the carbon spectrum.

Conclusion

Two isotopomeric forms of deuterated 3Z-hexenal, 3,4-$^2H_2$-3Z-hexenal (6) and 6,6,6-$^2H_3$-3Z-hexenal (3b), have been prepared by the oxidation of hexenol precursors with the Dess/Martin periodinane (1) in fluorotrichloromethane. While an alternative synthesis of (6) has been described[8], our current procedure is direct, high yielding and does not involve either high pressure hydrogenation or column chromatography.

Experimental

NMR spectra were recorded on a Bruker WP80SY (80 MHz.) spectrometer or a Joel GX270 (270MHz) in $CDCl_3$; data is reported in parts per million (δ) and is referenced to $CHCl_3$ at δ7.24 for ^1H spectra and δ77.0 for ^{13}C. GC was carried out using an HP 5830A gas chromatograph fitted with a 30m x 0.25mm ID SE30 Alltech Econo Cap™ column, 0.25μ film thickness, temperature programmed for 5min @ 40°C, 10°C/min, 5min @ 280°C, with 10psi N_2 head pressure. Retention times (rt) are reported in decimal minutes and purity as a % of total peak area excluding solvent. GCMS was carried out using an HP 5890 Series II gas chromatograph fitted with a 30m x 0.25mm ID DB1 column, 0.25μ film thickness, temperature programmed for 5min @ 40°C, 5°C/min, 20min @ 280°C, with 2psi He head pressure directly coupled to a VG70-250S mass spectrometer (VG Instruments, Manchester, UK) operating at 70eV.

All reagents [Aldrich Chemical Company, unless stated] were used without further purification unless stated. Dichloromethane [BDH] and fluorotrichloromethane (Freon 11) [E.I. Du Pont De Nemours & Co. (Inc.)] were freshly distilled from P_2O_5 under dry N_2. Ether was diethyl ether [BDH analar]. Room temperature was 18-22°C.

3Z-Hexenal (3a) (Method A, dichloromethane as solvent.)
3Z-Hexen-1-ol (2a) (84.6mg, 0.85mmol) was added at room temperature to a slurry of Dess-Martin periodinane (1)[18] (0.54g, 1.27mmol) in dichloromethane (10ml) and the mixture was stirred for 3hrs. Solid material was removed by filtration and the combined filtrate and rinsings (CH_2Cl_2, 2x15ml) were washed firstly with a solution of 0.5 M $Na_2S_2O_3.5H_2O$ in saturated $NaHCO_3$ (20ml), then water (20ml) and saturated brine (20ml). The organic phase was dried over $MgSO_4$, filtered and concentrated on a rotary evaporator under reduced pressure (450 mmHg) at 0°C to give (3a) as a clear mobile oil, (32.3mg, 39%), GC rt 8.09 (94%). ^1H NMR δ, 0.99 (3H, t, J=7.7Hz, CH_3-), 2.06

(2H, m, CH_3CH_2-), 3.17 (2H, dd, J=7.3Hz, J=1.5Hz, -CH_2-CHO), 5.46-5.75 (2H, m, -CH=CH-), 9.66 (1H, t, J=1.5Hz, -CHO). ^{13}C NMR δ, 13.7 (C-6), 20.7 (C-5), 42.5 (C-2), 117.5 (C-3), 137.1 (C-4), 199.2 (C-1). MS *m/z* rel. int. 98 (M^+, 11.4), 83 (20.0), 80 (11.8), 69 (36.4), 55 (28.9), 41 (100), 39 (27.9).

3Z-Hexenal (3a) (Method B, fluorotrichloromethane as solvent.)
3Z-Hexen-1-ol (2a) (84.6mg, 0.85mmol) was added at room temperature to a slurry of Dess-Martin periodinane (1)[16] (0.54g, 1.27mmol) in fluorotrichloromethane (15ml) and the reaction mixture was stirred for 18hrs. The slurry was filtered directly with rinsings (2x15ml $FCCl_3$) into a separating funnel and partitioned against a solution of 0.5 M $Na_2S_2O_3.5H_2O$ in saturated $NaHCO_3$ (30ml). The lower, organic phase was run off and the aqueous residue was re-extracted with a further 20ml of $FCCl_3$. The combined organic phases were dried ($MgSO_4$) and filtered through a sintered glass funnel pressurized by the freon vapour. $FCCl_3$ was removed by slow distillation under a blanket of dry N_2 (20ml/min) at atmospheric pressure in a rotary evaporator fitted with a dry-ice/acetone cold trap (water bath temperature at 24°C) to give (3a) as a clear mobile oil (71.3mg, 89%). GC rt 8.09 (96%). Data as above.

6,6,6-$^2H_3$-3Z-Hexenal (3b)
6,6,6-$^2H_3$-3Z-Hexen-1-ol (2b) (115.7mg, 1.12mmol) was oxidised with Dess/Martin periodinane (1) (0.713g, 1.68mmol) in fluorotrichloromethane (15ml) by method B to yield (3b) as a clear mobile oil (100.9mg, 89%) GC rt 8.13 (94%). ^{1}H NMR (270MHz) δ, 2.06 (2H, d, J=7Hz, CD_3CH_2-), 3.17 (2H, dd, J=7.3Hz, J=1.5Hz, -CH_2-CHO), 5.46-5.75 (2H, m, -CH=CH-), 9.65 (1H, t, J=1.5Hz, CHO). ^{13}C NMR (270MHz) δ, 20.8 (C-5), 42.5 (C-2), 117.5 (C-3), 137.1 (C-4), 199.2 (C-1). MS *m/z* rel. int. 101 (M^+, 33.2), 83 (34.6), 72 (84.3), 58 (29.3), 55 (38.2), 43 (100), 42 (93.2), 39 (30.7).

3,4-$^2H_2$-3Z-Hexen-1-ol (5)
3-Hexyn-1-ol (4) (0.898g, 9.15mmol) was added at room temperature to a slurry of Lindlar's catalyst (5% Pd on $CaCO_3$ poisoned with Pb) (0.25g) in pentane (20ml) and quinoline (0.2ml). The reaction flask was swept with D_2 gas (99.8% atom D) and the contents was stirred vigorously while the uptake of D_2 was monitored. An hydrogenation apparatus similar to that described by Vogel was used for this purpose[21]. After 1.5hrs, 220ml of D_2 (9.15mmol) had been consumed and (4) was no longer detectable by GC (rt 10.58). The reaction mixture was filtered through a plug of $CaCO_3$ and rinsed with ether (2x20ml). The filtrate was partitioned against 1.0M HCl saturated with NaCl (20ml), washed with saturated brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product as viscous, pale yellow oil. Short path distillation (Kugelrohr) gave (5) as a colourless oil (0.8076g, 86.4%), bp 55-60°C/14mmHg. GC rt 9.83 (>99%). ^{1}H NMR δ, 0.93 (3H, t, J=7.8Hz, CH_3-), 1.85-2.08 (3H, m, CH_3CH_2, -OH), 2.27 (2H, t, J=6.6Hz, -CH_2CH_2OH), 3.58 (2H, t, J=6.6Hz, -CH_2OH). ^{13}C NMR δ, 14.1 (C-6), 20.4 (C-5), 30.5 (C-2), 62.2 (C-1), 124.0 (t, C-3), 134.3 (t, C-4). MS *m/z* rel. int. 102 (M^+, 6.1), 84 (45.7), 83 (45.0), 71 (47.9), 69 (80.0), 68 (62.9), 57 (60.0), 43 (82.1), 42 (100), 31 (37.9).

3,4-$^2H_2$-3Z-Hexenal (6)

3,4-$^2H_2$-3Z-Hexen-1-ol (5) (0.4573g, 4.48mmol) was oxidised with Dess/Martin periodinane (1) (2.85g, 6.71mmol) in fluorotrichloromethane (15ml) by method B to yield (6) as a clear mobile oil (0.4168g, 92%) GC rt 8.15 (99%). ^{1}H NMR δ, 0.99 (3H, t, J=7.7Hz, CH_3-), 2.05 (2H, m, CH_3CH_2-), 3.18 (2H, bs, -CH_2CHO), 9.65 (1H, t, J=1.5Hz, -CHO). ^{13}C NMR δ, 13.8 (C-6), 20.7 (C-5), 42.3 (C-2), 199.4 (C-1), C-3 and C-4 not observed. MS *m/z* rel. int. 100 (M^+, 21.8), 85 (22.6), 82 (14.8), 71 (58.7), 57 (43.3), 43 (81.9), 42 (100), 40 (31.8).

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