The Synthesis of 6,6,6-$^2H_3$-2E-Hexenal.

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Summary

6,6,6-$^2H_3$-2E-Hexenal, leaf-aldehyde, has been synthesised in 45% yield and 99.3% purity by reaction of 3,3,3-$^2H_3$-*n*-propyl magnesium bromide with an ethereal solution of 3-trimethylsiloxy-2-propenal (3) prepared *in situ*. This new one pot procedure alleviates the need to isolate (3) and should prove useful in the synthesis of other E-α,β-unsaturated aldehydes.

Key Words: 6,6,6-$^2H_3$-2E-hexenal, 2E-hexenal, leaf aldehyde, synthesis, E-α,β-unsaturated aldehydes, deuterium.

Introduction

2E-Hexenal or 'leaf aldehyde'[1] occurs widely as a product of the enzymatic and oxidative degradation of unsaturated fatty acids in processed foods[2] and disrupted plant tissue[3,4] and is an important aroma constituent in a number of fruit, vegetables and leaves[3]. 2E-Hexenal is a key aroma impact compound in apples, pears, quinces[5] and freshly picked tea[6] and is also responsible for 'off' flavours found in processed kiwifruit products[7]. We required a practical synthesis of 6,6,6-$^2H_3$-2E-hexenal for use in the study of aroma biosynthesis.

The continued appearance of regiospecific routes to E-α,β-unsaturated aldehydes[8] indicates that synthetic interest in this class of compounds remains high. E-α,β-unsaturated aldehydes can be elegantly prepared[9] by the addition of Grignard reagents to 3-trimethylsiloxy-2-propenal (3). The commercial availability of regiospecifically deuterated alkyl halides, and hence access to the corresponding Grignards, suggested this strategy as suitable for the synthesis of 6,6,6-$^2H_3$-2E-hexenal.

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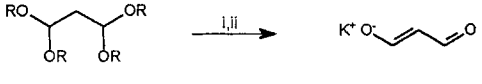
Results and Discussion

Potassium malondialdehyde (2)[10] is readily accessible by the hydrolysis of 1,1,3,3-tetraalkoxypropanes (1) with dilute acid and enolization of the resultant dialdehyde with aqueous potassium hydroxide (Scheme 1). Both tetramethoxy- and tetraethoxypropane gave the potassium salt (2) as a yellow to pale orange, amorphous solid in good yield; 68% and 75% respectively.

Treatment of anhydrous potassium malondialdehyde in dry ether with an excess of trimethylsilyl chloride (TMSCl) in the presence of triethylamine, is reported[9,11] to give 3-trimethylsiloxy-2-propenal (3), in a 63-69% yield as a yellow oil stable enough to be distilled under vacuum. In our hands however, (3) underwent significant decomposition on vacuum distillation and was not isolated in useful quantities. To avoid the isolation of (3), the silylation of (2) was modified by the addition of a catalytic quantity of N,N-dimethylaminopyridine (DMAP), a reduction in the concentration of triethylamine and the use of only a small molar excess of TMSCl. These changes were effective in generating an ethereal solution of (3) which could be used directly in subsequent reactions. (Scheme 2)

Scheme 1. **Preparation of Potassium Malondialdehyde.**[10]



(1) (2)

i, HCl (2N) 50 °C ii, KOH (5N)

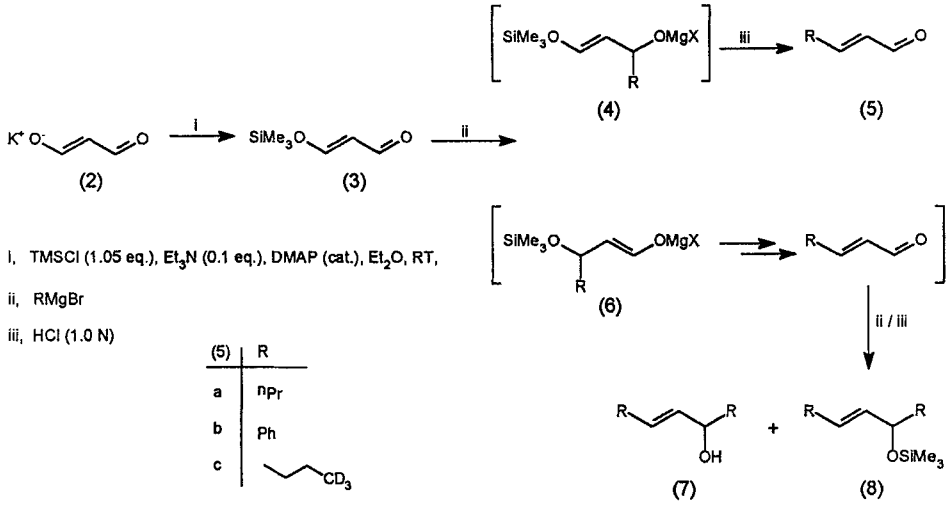
R = Me, 68%. R = Et, 75%.

The direct addition of *n*-propyl magnesium bromide to an ethereal solution of (3) at room temperature gave 2E-hexenal (5a) in 34% yield after chromatography with a purity >98% by GC. Alkenes (7a) and (8a) (Scheme 2) were also isolated and characterised. Formation of (7a) and (8a) was consistent with the 1,4-addition of Grignard reagent to (3) prior to hydrolysis. The moderate yields of 2E-hexenal isolated under these conditions stem in part from the volatility of the product (B.p. 43°C @ 12mmHg[12]); a problem of particular significance when concentrating fractions under reduced pressure obtained from flash chromatography. Losses were minimised with the use of low boiling point chromatography solvents, i.e. petrol ether (b.p. 30-40°C) and dichloromethane. However even with the careful removal of solvent below room temperature, recoveries of standard solutions were poor, typically 60%. Furthermore attempts to purify freshly chromatographed 2E-hexenal by distillation

under reduced pressure resulted in significant oxidation to the corresponding acid, typically lowering the purity to 85% by GC. The low yields of 2E-hexenal may not however be attributable *solely* to the volatility and lability of this aldehyde. Indeed treatment of an ethereal solution of (3) with phenyl magnesium bromide gave the less volatile *trans*-cinnamonaldehyde (5b)[13] in only 19% yield.

Use of the bulkier silylating agents *tert*-butyldimethylsilyl chloride and *tert*-butyldiphenylsilyl chloride successfully reduced formation of (7) and (8) but also reduced the yield of 2E-hexenal (Table 1).

Scheme 2. **Synthetic Route to 2E- enals.**



Addition of *n*-propyl magnesium bromide to an ethereal solution of (3) cooled to -78°C, gave an increased yield of 2E-hexenal (44.3%), with a corresponding reduction in the formation of both (7) and its silylated derivative (8). Using these conditions, addition of 3,3,3-$^2H_3$- to a solution of (3), gave 6,6,6-$^2H_3$-2E-hexenal (5c) in 45.1% yield after flash chromatography with 99.3% purity by GC.

Yields of labelled and unlabelled 2E-hexenal obtained from this modified procedure compared favourably with those reported by Ullrich *et. al.*[9] for other aliphatic 2E-enals. (2E-Hexenal was not prepared by Ullrich *et. al.*[9]) The development of this 'one pot' synthesis of E-α,β-unsaturated aldehydes eliminates the need to isolate the thermally unstable siloxy acrolein (3). Furthermore we feel this modified procedure will be generally applicable to the synthesis of other E-α,β-unsaturated aldehydes in both labelled and unlabelled form.

Table 1. Yields of 2E-enals.

Silylating Agent	Grignard Reagent RMgBr	Temp/ °C	Product Ratio[a] (5)	(7)	%E[a] isomer	% Yield aldehyde[b]
TMSCl	R=^{n}Pr	rt	1.0	0.17	98.7	34.0
TMSCl	R=^{n}Pr	-78	1.0	0.16	99.3	44.3
t-BDMSCl[c]	R=^{n}Pr	rt	1.0	0.03	98.8	19.0
t-BDPSCl[d]	R=^{n}Pr	rt	1.0	0.08	98.5	12.4
TMSCl	R=Ph	-78	1.0	0.91	>99.9	18.9
TMSCl	R=$CH_2CH_2C^2H_3$	-78	1.0	0.17	99.3	45.1

[a] Determined by GC.
[b] After flash chromatography.
[c] *tert*-butyldimethylsilylchloride.
[d] *tert*-butyldiphenylsilylchloride.

Experimental.

NMR spectra were recorded on a Bruker WP80SY (80 MHz.) spectrometer in $CDCl_3$. NMR data is reported in parts per million (δ) and referenced to $CHCl_3$ at δ7.24 and δ77.0 for ^1H and ^{13}C spectra respectively. GC-MS 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 program, 5min @ 40°C, 5°C/min, 20min @ 280°C, 2 psi He head pressure directly coupled to a VG70-250S mass spectrometer operating at 70eV. Retention times (rt) are reported in minutes.

All reagents (Aldrich Chemical Company) were used without further purification unless stated. Ether is diethyl ether (BDH Analar). Dry ether is diethyl ether, freshly distilled from sodium/benzophenone 'blue' under dry nitrogen. Room temperature (RT) is 18-23°C. All experiments were carried out under an atmosphere of dry N_2.

Tlc was performed on foil backed silica gel plates (0.2mm) (Merck Art. 5554), developed with freshly distilled 30-40 petrol ether (BDH) / dichloromethane (Univar) (2:1) and visualized by lightly spraying with a solution of vanillin (1.0g) in conc. H_2SO_4 (50ml) and charing at 150°C. Preparative column chromatography was carried out using 40μm (flash) silica gel (Alltech Associates Inc.) with the solvent system described above.

Ethereal Solution of 3-Trimethylsiloxy-2-propenal. (3)

Freshly distilled trimethylsilylchloride (TMSCl) (1.21ml, 9.53mmol) was added dropwise to a stirred slurry of potassium malondialdehyde (1.0g, 9.08mmol) and N,N-dimethylaminopyridine (catalytic) in dry ether (20.0 ml) and freshly distilled triethylamine (0.13ml, 0.91mmol) at RT over a 10 minute period. The reaction was stirred continuously for 24 hrs. to give an ethereal solution of (3).

Reaction of *n*-propyl magnesium bromide with (3).

n-Bromopropane (0.83ml, 9.08mmol) was added to a suspension of magnesium turnings (0.2427g, 9.98mmol) and iodine (<1mg, catalytic) in dry ether at a rate sufficient to maintain a gentle reflux. The solution was stirred at RT for a further hour then added to an ethereal solution of (3)

(9.08mmol) cooled to -78°C [CO_2/acetone]. The reaction mixture was warmed to RT over 30 mins. and quenched with dilute hydrochloric acid (1N, 20ml). The two phases were separated and the aqueous layer was extracted with ether (2x30ml). The combined ethereal phases were washed with water (50ml), brine (30ml), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, with care in an ice/water bath, to afford a crude oil. Tlc analysis showed 3 components were present (R_f 0.08, 0.26 and 0.64). Flash silica gel chromatography yielded 3 fractions.

5E-Nonen-4-ol. (7a) Clear viscous oil (0.0805g), R_f 0.08. ^{1}H NMR δ, 0.85 (6H, br t, J=7.5Hz, 2x -CH_3), 1.08-1.58 (6H, m, CH_3CH_2-, $CH_3CH_2CH_2$-), 1.74 (1H, br s, -OH), 1.96 (2H, br q, J=7.5Hz, -CH_2-CH=), 3.95 (1H, br q, J=5.9Hz, CHOH), 5.23-5.78 (2H, m, -CH=CH-). ^{13}C NMR δ, 13.5 (C-9), 13.9 (C-1), 18.6 (C-2), 22.2 (C-8), 34.2 (C-7), 39.5 (C-3), 72.7 (C-4), 131.5 (C-6), 133.4 (C-5). GCMS rt 15.1 min., (*m/z* rel. int.) 142 (M^+, 1.6), 124 (6.1), 99 (52.5), 57 (100).

2E-Hexenal. (5a) Clear mobile oil, (0.3942g, 44.3%), R_f 0.26. ^{1}H NMR δ, 0.90 (3H, t, J=7.6Hz, CH_3), 1.49 (2H, sextet, J=7.3Hz, CH_3CH_2-), 2.26 (2H, br q, J=7.7Hz, -CH_2-CH=), 6.04 (1H, ddt, J=15.6Hz, J=7.7Hz, J=1.4Hz, =CH-CHO), 6.79 (1H, dt, J=15.6Hz, J=6.6Hz, CH_2-CH=), 9.44 (1H, d, J=7.7Hz, -CHO). ^{13}C NMR δ, 13.3 (C-6), 21.0 (C-5), 34.5 (C-4), 133.0 (C-2), 158.1 (C-3), 193.6 (C-1). GCMS rt 11.1 min., (*m/z* rel. int.) 98 (M^+, 26.4), 97 (8.9), 83 (52.2), 69 (41.4), 57 (37.8), 55 (37.9), 41 (100).

4-Trimethylsiloxy-5E-nonene. (8a) Clear mobile oil (0.0173), R_f 0.64. ^{1}H NMR δ, 0.08 (9H, s, -$Si(CH_3)_3$), 0.89 (6H, br t, J=7.5Hz, 2x -CH_3), 1.09-1.60 (6H, m, CH_3CH_2-, $CH_3CH_2CH_2$-), 1.98 (2H, br q, J=7.5Hz, -CH_2-CH=), 4.00 (1H, br q, J=5.5Hz, CHOH), 5.19-5.71 (2H, m, -CH=CH-). ^{13}C NMR δ, 0.4 (C-1'), 13.6 (C-9), 14.0 (C-1), 18.8 (C-2), 22.4 (C-8), 34.2 (C-7), 40.6 (C-3), 73.6 (C-4), 130.3 (C-6), 133.8 (C-5). GCMS rt 18.0 min., (*m/z* rel. int.) 199 (5.4), 171 (100), 129 (29.6), 75 (51.4), 73 (66.4).

6,6,6-$^2H_3$-2E-Hexenal. (5c)

3,3,3-$^2H_3$-*n*-propyl magnesium bromide [prepared as above from 3,3,3-$^2H_3$-*n*-propyl bromide (MSD Isotopes, >99%$^2H_3$), (0.85ml, 9.08mmol)] was added to an ethereal solution of (3) cooled to -78°C [CO_2/acetone]. The reaction mixture was warmed to RT over 30 mins. and quenched with dilute hydrochloric acid (1N, 20ml). The two phases were separated and the aqueous layer was extracted with ether (2x30ml). The combined ethereal phases were washed with water (50ml), brine (30ml), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, with care in an ice/water bath, to afford a crude oil. Flash chromatography gave (5c) as a clear mobile oil, (0.4141g, 45.1%), R_f 0.26. ^{1}NMR δ, 1.42 (2H, br t, 7.3Hz, CD_3CH_2-), 2.22 (2H, br q, J=7.7Hz, -CH_2-CH=), 6.01 (1H, ddt, J=15.6Hz, J=7.7Hz, J=1.4Hz, =CH-CHO), 6.77 (1H, dt, J=15.6Hz, J=6.6Hz, CH_2-CH=), 9.41 (1H, d, J=7.7Hz, -CHO). ^{13}C NMR δ, 12.5 (bm, C-6), 20.7 (C-5), 34.4 (C-4), 133.0 (C-2), 158.3 (C-3), 193.7 (C-1). GCMS rt 10.9 min., (*m/z* rel. int.) 101 (M^+, 63.1), 100 (22.1), 99 (1.0), 98 (0.5), 83 (94.8), 72 (54.1), 69 (43.8), 58 (70.3), 55 (84.1), 45 (100).

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13. Identical to a commercial sample of *trans*-cinnamonaldehyde by MS and ^{1}H NMR.