SYNTHESIS OF DEUTERIUM LABELLED HEXENOLS

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SUMMARY

Hexenols are important flavour components of fruit and vegetables. We report the synthesis of *cis*-3-hexen-1-ol-6,6,6-$^2H_3$, hexan-1-ol-6,6,6-$^2H_3$, *cis*--2-hexen-1-ol-6,6,6-$^2H_3$ and *trans*-2-hexen-1-ol-6,6,6-$^2H_3$.

KEYWORDS

cis-3-hexen-1-ol-6,6,6-$^2H_3$, hexan-1-ol-6,6,6-$^2H_3$, *cis*-2-hexen-1-ol-6,6,6-$^2H_3$, *trans*-2-hexen-1-ol-6,6,6-$^2H_3$, flavour components, fruit volatiles

INTRODUCTION

Unsaturated hexanols are important components and intermediates in the flavour volatiles produced by fruit and vegetables. The production and metabolism of these compounds is mediated by complex multi-enzyme systems. A full knowledge of the chemical mechanisms and enzyme activities of these pathways is essential for an understanding of the origins and characteristics of the flavours of food constituents. Of particular interest to this research group are the six-carbon primary aroma compounds formed by enzymatic means from linolenic and linoleic acids[1]. Thus the synthesis of the deuterium labelled precursors; *cis*-3-hexen-1-ol-6,6,6-$^2H_3$, hexan-1-ol-6,6,6-$^2H_3$, *cis*-2-hexen-1-ol-6,6,6-$^2H_3$ and *trans*-2-hexen-1-ol-6,6,6-$^2H_3$ was undertaken in order to incorporate these precursors into the biochemical system of living fruit tissue.

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DISCUSSION

The key step in the synthesis of *cis*-3-hexen-1-ol-6,6,6-$^2H_3$ and hexan-1-ol-6,6,6-$^2H_3$ involved the alkylation of the acetylide anion of the tetrahydropyranyl (THP) ether of 3-butyn-1-ol with 1-bromoethane-2,2,2-$^2H_3$ (Scheme 1).[2] The anion was generated by treating protected alcohol (1) with lithamide in liquid ammonia. Subsequent addition of the deuterated bromoethane followed by removal of the THP protecting group with methanol and amberlite resin afforded 3-hexyn-1-ol-6,6,6-$^2H_3$ (2) in 71% overall yield after purification by flash chromatography.[3]

Partial hydrogenation of alkynol (2) over Lindlar catalyst in 4:1 hexane/ethyl acetate at room temperature for 3 hours, gave *cis*-3-hexen-1-ol-6,6,6-$^2H_3$ (3) in 73% yield after purification. The ^1H NMR spectrum of alkenol (3) was consistent with the assignment of *cis*- stereochemistry about the double bond in that irradiation of the allylic protons (H-2) at δ_H 2.33 collapsed the multiplet at δ_H 5.29-5.39 to a doublet $J_{3,4}$ 11 Hz.

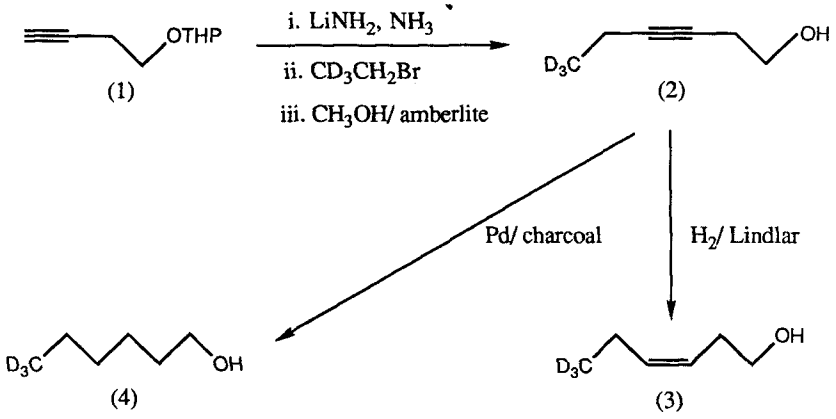
Hydrogenation of alkynol (2) was effected using 5% palladium on charcoal giving hexan-1-ol-6,6,6-$^2H_3$ (4) in 40% yield after purification by flash chromatography. In this case, the molecular ion at m/z 105 in the mass spectrum, was consistent with the desired product.

In a similar fashion, *cis*- and *trans*-2-hexen-1-ol-6,6,6-$^2H_3$ were prepared from the acetylenic alcohol (5) (Scheme 2). In this case the anion generated from the THP ether of 2-propyn-1-ol with lithamide in liquid ammonia, was treated with 1-bromopropane-3,3,3-$^2H_3$ followed by removal of the THP protecting group with methanol and amberlite resin to afford 2-hexyn-1-ol-6,6,6-$^2H_3$ (6) in 77% overall yield after purification.

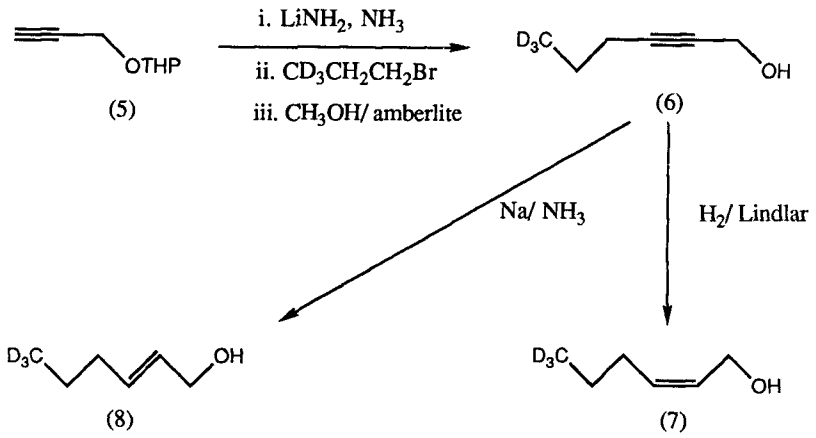
syn-Hydrogenation of alkynol (6) using Lindlar catalyst in 4:1 hexane/ ethyl acetate at room temperature for 3 hours gave *cis*-2-hexen-1-ol-6,6,6-$^2H_3$ (7) in 70% yield after purification by flash chromatography. The *cis*-stereochemistry of the double bond of alkenol (7) was confirmed by ^1H NMR spectroscopy. Irradiation of the allylic protons (H-1) at δ_H 4.20 simplified the multiplet at δ_H 5.49-5.67 allowing the vinylic coupling constant $J_{2,3}$ 9.9 Hz to be obtained.

trans-2-Hexen-1-ol-6,6,6-$^2H_3$ (8) was prepared in 63% yield by reduction of alkynol (6) with sodium and liquid ammonia. Irradiation of the allylic protons (H-1) at δ_H 4.08 in the ^1H NMR spectrum, collapsed the multiplet at δ_H 5.60-5.73

to a doublet at δ_H 5.65 ($J_{2,3}$ 16 Hz) and a multiplet at δ_H 5.71. The magnitude of the vinylic coupling constant $J_{2,3}$ 16 Hz established the *trans*-stereochemistry of the double bond.



Scheme 1:



Scheme 2:

EXPERIMENTAL

General:- ^1H Nuclear magnetic resonance (NMR) spectra were obtained at 270 MHz using a Jeol GX 270 spectrometer. ^1H NMR data are expressed in parts per million downfield from tetramethylsilane as an internal reference and are reported as positions (δ_H), relative integral, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet), coupling constant (J Hz) and assignment. ^{13}C NMR spectra were obtained at 67.8 MHz on a Jeol GX 270 spectrometer.

Mass spectra were recorded on a VG70-250S double focusing magnetic sector mass spectrometer with an ionisation potential of 70 eV. Major fragmentations are given as percentages relative to the base peak intensity.

Flash chromatography was performed according to the procedure of Still *et al*[3] using Merck Kieselgel 60 (230-400 mesh) with hexane/ethyl acetate eluent. Compounds were visualised by vanillin in methanolic sulfuric acid.

Solvents were purified and dried according to the methods of Perrin, Perrin and Armarego[4].

1-Bromoethane-2,2,2-$^2H_3$, 98% D and 1-bromopropane-3,3,3-$^2H_3$, 98% D were purchased from Merck Chemical Company.

2-(3-Butyn-1-yloxy)-tetrahydro-2H-pyran (1)

Dihydropyran (4.5 g, 53 mmol) was added to a solution of 3-butyn-1-ol (2.5g, 36 mmol) in dichloromethane (50 ml). Camphorsulphonic acid (catalytic quantity) was added and the mixture stirred at room temperature for 16 hours. The solvent was removed at reduced pressure to give a yellow oil that was purified by flash chromatography using 9:1 pentane/diethyl ether as eluent to give the THP ether (1) (4.42g, 80% yield) as a colourless liquid, bp 53°C/3 mm Hg (lit.[5] bp 51°C/2 mm Hg).

3-Hexyn-1-ol-6,6,6-$^2H_3$ (2)

A solution of THP ether (1) in THF (25 ml) was added over 30 minutes to lithamide prepared from lithium (0.21 g, 30 mmol) in liquid ammonia (70 ml) with ferric nitrate (3 mg). After stirring for 1 h, a solution of 1-bromoethane-2,2,2-$^2H_3$ (1.63 g, 15 mmol) in THF (15 ml) was slowly added over 1h. The solution was stirred overnight at -35°C then quenched with saturated ammonium chloride solution (10 ml). The reaction mixture was extracted with ether (3 x 70 ml), washed with brine (2 x 30 ml), and dried over $MgSO_4$. Removal of solvent at reduced pressure afforded a pale yellow oil which was dissolved in methanol (30 ml) and stirred overnight with camphorsulphonic acid (catalytic quantity). Removal of the solvent at reduced pressure gave a yellow oil that was purified by flash chromatography using 4:1 hexane/ethyl acetate to give 3-Hexyn-1-ol-6,6,6-$^2H_3$ (2) as a colourless oil (1.08 g, 71%) δ_H (270 MHz, $CDCl_3$) 1.87 (1H, br.s, OH),

2.16 (2H, br.s, CD_3-$\underline{CH_2}$),2.40-2.46 (2H, m, C≡C$\underline{CH_2}CH_2OH$) and 3.68 (2H, t, J 6.2 Hz, $\underline{CH_2}OH$); δ_C (67.8 MHz, $CDCl_3$) 12.1, 23.1, 61.3, 75.6, 84.1 and 96.3.

cis-3-Hexen-1-ol-6,6,6-$^2H_3$ (3)

A mixture of 3-hexyn-1-ol-6,6,6-$^2H_3$ (2) (700 mg, 6.90 mmol), triethylamine (1 drop) and Lindlar catalyst (10 mg) in 4:1 hexane/ethyl acetate (25 ml) was stirred at room temperature under a balloon of hydrogen for 16 hours. The catalyst was removed by filtration and the solvent evaporated at reduced pressure to afford a yellow oil that was purified by flash chromatography using 2:1 hexane/ethyl acetate as eluent to give *cis*-3-hexen-1-ol-6,6,6-$^2H_3$ (3) as a colourless oil (530 mg, 73%) δ_H (270 MH_z, $CDCl_3$) 1.41 (1H, br.s, OH), 2.06 (2H, d, J 7 Hz, CD_3-$\underline{CH_2}$), 2.33 (2H, q, J 6.5 Hz, CD_3CH_2C=C$\underline{CH_2}$), 3.65 (2H, t, J 6.4 Hz, $\underline{CH_2}$-OH), 5.29-5.39 (1 H, m, H-3) and 5.55 - 5.62 (1H, m, H-4); m/z 103 (1), 85 (20), 67 (9), 57 (100), 41 (20) and 31 (9).

Hexan-1-ol-6,6,6-$^2H_3$ (4)

To a solution of 3-hexyn-1-ol-6,6,6-$^2H_3$ (2) (600 mg, 5.94 mmol) in 1:1 pentane/diethyl ether was added 5% palladium on charcoal (2 mg). The mixture was stirred overnight at room temperature under a balloon of hydrogen. After removal of the catalyst by filtration, the solvent was evaporated at reduced pressure to afford a yellow oil that was purified by flash chromatography using 2:1 hexane/ethyl acetate as eluent to give hexan-1-ol-6,6,6-$^2H_3$ (4) as a colourless oil (250 mg, 40%) δ_H (270 MHz, $CDCl_3$) 0.87-0.89 (2H, m, CH_2),1.30-1.59 (7H, m, 3 x CH_2 and OH) and 3.64 (2H, t, J 6.6 Hz, $\underline{CH_2}OH$); m/z 105 (1), 87 (7), 72 (14), 59 (100), 43 (56) and 31 (43).

2-(2-Propynyloxy)tetrahydro-2H-pyran (5)

To a solution of 2-propyn-1-ol (10.0g, 0.18 mol) and dihydropyran (15.1g, 0.18 mol) was added concentrated hydrochloric acid (2 drops). The mixture was allowed to stand for 3 hours with occasional shaking. Diethyl ether was then added and the mixture shaken vigorously with 10% aqueous sodium hydroxide. The organic layer was separated and dried over $MgSO_4$. Concentration, followed by

distillation at reduced pressure, afforded THP ether (5) (18.3g, 73%) as a colourless liquid, bp 80°C/15 mm Hg (lit.[6] bp 40-43°C/1 mm Hg).

2-Hexyn-1-ol-6,6,6-$^2H_3$ (6)

A solution of THP ether (5) (1.54 g, 11 mmol) in THF (25 ml) was added over 30 minutes to lithamide prepared from lithium (0.15 g, 22 mmol) in liquid ammonia (60 ml) using ferric nitrate (catalytic quantity). After stirring for 1 h, a solution of 1-bromopropane-3,3,3-$^2H_3$ (1.50 g, 12 mmol) in THF (15 ml) was slowly added over 1h. The solution was stirred overnight at -35 °C then quenched with saturated ammonium chloride solution (10 ml). The reaction mixture was extracted with ether (3 x 70 ml), washed with brine (2 x 20 ml) and dried over $MgSO_4$. Removal of solvent at reduced pressure afforded a yellow oil. The oil was dissolved in methanol (25 ml) and stirred overnight with camphorsulphonic acid (catalytic quantity). Evaporation of the solvent under reduced pressure and purification by flash chromatography using 4:1 hexane/ethyl acetate gave 2-hexyn-1-ol-6,6,6-$^2H_3$ (6) as a colourless oil (860 mg, 77% yield) δ_H (270 MHz, $CDCl_3$) 1.52 (3H, t, J 7 Hz, D_3C-$\underline{CH_2}$), 1.73 (1H, br.s, OH), 2.16-2.23 (2H, m, $\underline{CH_2}C{\equiv}C$) and 4.26 (2H, br.s, $\underline{CH_2}OH$); m/z 100 (12), 83 (100), 71 (34), 55 (60), 43 (36), 41 (37) and 39 (39).

cis-2-Hexen-1-ol-6,6,6-$^2H_3$ (7)

A mixture of 2-hexyn-1-ol-6,6,6-$^2H_3$ (6) (200 mg, 2 mmol), triethylamine (1 drop) and Lindlar catalyst (10 mg) in 4:1 hexane/ethyl acetate (25 ml) was stirred at room temperature for 16 hours under a balloon of hydrogen. The catalyst was removed by filtration and the solvent evaporated to afford a yellow oil that was purified by flash chromatography using 2:1 hexane/ethyl acetate as eluent to give *cis*-2-hexen-1-ol-6,6,6-$^2H_3$ (7) as a pale yellow oil (145 mg, 70%) δ_H (270 MHz, $CDCl_3$) 126 (1H, br.s, OH), 1.38 (2H, t, J 7.3 Hz, $D_3C\underline{CH_2}$), 2.04 (2H, q, J 7 Hz, $\underline{CH_2}C{=}C$), 4.20 (2H, d, J 6 Hz, $\underline{CH_2}OH$) and 5.49-5.67 (2H, m, H-2 and H-3); m/z 100 (16), 83 (100), 71 (43), 55 (88), 43 (55), 39 (49) and 29(49).

trans-2-Hexen-1-ol-6,6,6-$^2H_3$ (8)

A solution of 2-hexyn-1-ol-6,6,6-$^2H_3$ (6) (500 mg, 4.95 mmol) in anhydrous diethyl ether (30 ml) was added dropwise to a solution of sodium (500

mg, 21.7 mmol) in liquid ammonia (60 ml). The reaction was stirred at -35 °C for 14 h then quenched with saturated ammonium chloride solution (10 ml). Diethyl ether (50 ml) was added and the ammonia allowed to evaporate. After further dilution with ether (100 ml) the organic layer was separated and dried over $MgSO_4$. Removal of solvent at reduced pressure afforded a yellow oil which was purified by flash chromatography using 2:1 hexane/ethyl acetate as eluent, to give *trans*-2-hexen-1-ol-6,6,6-$^2H_3$ (8) as a colourless oil (320 mg, 63% yield) δ_H (270 MHz, $CDCl_3$) 1.39 (2H, t, J 7.3 Hz, $D_3C\underline{CH_2}$), 1.53 (1H, br.s, OH), 1.99-2.06 (2H, q, J 6.6 Hz, $\underline{CH_2}C{\equiv}C$), 4.08 (2H, J 4.4 Hz, CH_2OH) and 5.60-5.73 (2H, m, H-2 and H-3); m/z : 103 (M^+; 2), 85 (16), 57 (100), 43 (19), 39 (10) 31 (8).

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