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SYNTHESIS OF DEUTERATED 4-HYDROXYALKENALS

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***ABSTRACT:** A concise and isotope specific synthesis of deuterated analogs of 4-hydroxyalkenals is reported.*

4-Hydroxyalkenals have been reported as the most cytotoxic products of lipid peroxidation.[1] There is considerable interest in tissue analysis of 4-hydroxyalkenals since lipid peroxidation is thought to play a role in many diseases.[2] Analytical methods exist to quantitate the lipid peroxidation products in tissues, and a recent review suggests the most promising method is based on tandem derivatization to form the pentafluorobenzyl (PFB) oxime and TMS ether, followed by negative ion

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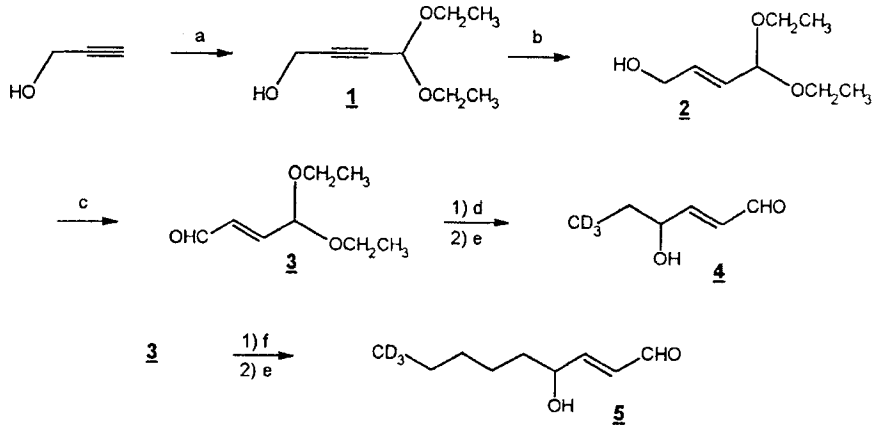

a) EtMgBr, $HC(OEt)_3$ b) $LiAlH_4$ C) Swern Oxidation
d) CD_3CH_2MgI e) H_3O^+ f) $CD_3CH_2CH_2CH_2CH_2MgBr$

FIGURE 1.

chemical ionization (CI) gas chromatography-mass spectrometry (GC-MS).[3] While the GC-MS method allows detection at sub-picogram levels, it requires an isotopically labelled internal standard for quantitation. Initially 2,3-dideutero-4-hydroxyalkenals were synthesized by reduction of a triple bond precursor with $LiAlD_4$.[4,5] This standard was of limited use because of observed deuterium exchange (D.W. Thomas, R.J. Stephens, and F.J.G.M. van Kuijk, unpublished results). A different internal standard was synthesized with the deuterium labels at the terminal carbon as shown in **FIGURE 1.**

A recent review demonstrates four separate approaches to the synthesis of these alkenals.[1] Several of these approaches are not practical when isotope labeling is brought into consideration, since the isotope should be introduced into the synthetic scheme as late as possible. The synthesis reported here provides the flexibility of a common intermediate that allows late introduction of any nucleophile

with or without isotopic labels (D, ^{13}C, ^{14}C, T). It is facilitated by commercial availability of terminally labeled deuterated alkyl halides and easily obtainable starting materials.

The synthesis began with carbon alkylation of propargyl alcohol with triethylorthoformate to produce 1,1-diethoxy-2-butyn-4-ol, 1.[6] The use of an orthoformate served the useful purpose of adding to the carbon skeleton an aldehyde preprotected as the diethyl acetal. The yield of this alkylation is marginal because of the lower electrophilicity of the orthoformate and the competition between oxygen and carbon nucleophiles. The low yield is only tolerable because it's used in the initial stages of the synthesis and it eliminates protection and deprotection sequence of the alcohol. The alkyne was then reduced stereospecifically to a trans alkene with $LiAlH_4$ in THF providing trans-1,1-diethoxy-2-butene-4-al, 2, in high yield.[7] The alcohol was oxidized to the aldehyde, 3, following the procedure of Swern.[8] This key intermediate, trans-4,4-diethylacetal-2-butenal, 3, was treated with Grignard reagents produced from 2,2,2-trideuteroethyl iodide and 5,5,5-trideuteropentyl bromide, respectively. The resulting allylic alcohols were subjected to mild acid hydrolysis, without isolation of the acetals, to give the corresponding alkenals, trans-4-hydroxy-6,6,6-trideutero-2-hexenal, 4, and trans-4-hydroxy-9,9,9-trideutero-2-nonenal, 5, respectively.

Experimental:

Unless otherwise noted, reagents were obtained from commercial suppliers and were used without further purification. Diethyl ether and THF were distilled from sodium/benzophenone ketyl immediately preceding use. Deuterium labeled alkyl halides were obtained from MSD isotopes. All reactions using organometallic reagents were conducted

under a dry Argon atmosphere with oven dried glassware. Gas chromatography was performed on a Perkin Elmer 3920B equipped with a FID detector. A 15m Megabore DB-5 column was used with He carrier gas. Flash chromatography was performed with Silica gel (grade 60) 230-400 mesh average particle size provided by Aldrich. The TLC plates used were aluminum backed, UV_{254}, 250 micron layer supplied by Whatman. NMR spectra were obtained on a Bruker AC-300 or Bruker AM-500 spectrometers with a 5mm dual band probehead. High resolution (HR) and chemical ionization (CI) mass spectroscopy were obtained on a VG 7070E-HF mass spectrometer.

1,1-Diethoxy-2-butyn-4-ol (1):

Prepared by standard literature procedure.[6]

trans-1,1-Diethoxy-2-butene-4-ol (2):

To a solution of 0.17g $LiAlH_4$ (1.0 eq.) in 5.0 mL dry ether at -25° C over argon atmosphere was added slowly with stirring 0.50g of 1 (0.60 eq.). Stirring was continued for 6 hr while maintaining the temperature at -25° C. The reaction was quenched with saturated aqueous NH_4OH. During the quench, the temperature was kept at or below -5° C. After filtration of the slurry, the remaining precipitate was washed with water, followed by ether. The aqueous layer was extracted three times with ether. The combined extracts were dried over anhydrous $MgSO_4$, the drying agent removed by filtration, and the remaining ether solution concentrated via rotary evaporation. Flash chromatography (1:1 hexane / Ethyl acetate) yielded 0.41g yellow oil (87%). Spectral information is identical to literature.[9]

trans-1,1-Diethoxy-2-butene-4-al (3):

Oxalyl chloride (7.6g) was placed in 110 mL of CH_2Cl_2 at -78° C. Dry DMSO (9.3 mL in 25 mL CH_2Cl_2) was added slowly over a period of 50

min. After the addition was complete the reaction was stirred for 20 additional minutes. Alcohol **2** was added (7.0g, 0.044 moles) dropwise over a period of 1 hr and the mixture stirred for another hr at -78° C. Triethyl amine (27g) was added dropwise and the resulting mixture stirred for 1 hr. The cold bath was then removed and reaction mixture poured into 50 mL of water and 150 mL ether. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined and washed with water and saturated brine, then dried over $MgSO_4$. Drying agent was removed by filtration and the resulting organic solution was concentrated via rotary evaporation to give 69% yield by GLC. Distillation (48-52° @ 0.70mm Hg) yielded 2.6g product (37% isolated yield).

^{1}H NMR: ($CDCl_3$) 1.20-1.22 (6H,t); 3.50-3.67 (4H,m); 5.11-5.13 (1H,d); 6.29-6.37 (1H,dd); 6.61-6.68 (1H, dd); 9.58-9.60 (1H,d)

^{13}C NMR: ($CDCl_3$) 15.15(q); 61.71(t); 99.17(d); 133.62(d); 151.25(d); 193.12(s)

MS: (CI^+) m/e (% abundance): 159 (M^+,11); 131 (3); 129 (10); 114 (11); 113 (100); 103 (8); 101 (5); 97 (2).

HRMS: (CI^+) Calculated for $C_8H_{14}O_3$ 158.0943; Found 158.0968.

General procedure for Grignard reactions:

Powdered Mg (30 mg) was placed in 2.0 mL of dry ether under argon atmosphere at RT. To this was added 0.13 ml of 3,3,3-5-trideuteroethyl iodide at a rate to allow the ether to reflux. When the addition of alkyl halide was completed, another 3.0 mL of dry ether was added to increase the reaction volume. The reaction mixture was stirred for 15 min and then the aldehyde **3** (0.23 mL in approximately one mL of dry ether) was added to the reaction. After stirring for 30 min, the reaction was quenched with saturated NH_4Cl. After extractions (three times with CH_2Cl_2), the organic phase was dried over anhydrous $MgSO_4$. The

solvent was removed via rotary evaporator. The crude product was taken directly to the next step.

General procedure for acetal hydrolysis:

The crude acetal (0.5 g approximately) was stirred in 50 mL of a 1:1 water/THF solution containing one drop of HCl at RT overnight. The THF was removed via rotary evaporation and the remaining aqueous layer was extracted three times with ether. The combined ether extracts were dried over $MgSO_4$, filtered from the drying agent, and the solvent removed on a rotary evaporator. The crude yield was 70-85%.

trans-4-hydroxy-6,6,6-Trideutero-2-hexenal (4):

^{1}H NMR: ($CDCl_3$) 1.55-1.67 (2H,m); 2.10 (1H,s br); 4.31-4.35 (1H,m); 6.23-6.32 (1H,dd); 6.76-6.83 (1H,dd); 9.53-9.56 (1H,d)

^{13}C NMR: ($CDCl_3$) 9.23 (3D br); 29.28 (t); 72.22 (d); 130.94 (d); 158.41 (d); 193.34 (d).

MS: (CI^+) m/e (%abundance): 118 (M^+,100); 117 (4); 116 (11); 115 (1); 102 (3); 101 (6); 100 (71); 99 (11); 98 (3).

HRMS: (CI^+) Calculated for M^+ $C_6H_8O_2D_3$ 118.0944.; Found 118.0940.

trans-4-hydroxy-9,9,9-Trideutero-2-nonenal (5):

^{1}H NMR: ($CDCl_3$) 1.12-1.45 (6H,m); 1.52-1.60 (2H,m); 2.81 (1H, s, br); 4.33-4.38 (1H, dd); 6.19-6.28 (1H,dd); 6.75-6.82 (1H,dd); 9.48-9.50 (1H,d)

^{13}C NMR: ($CDCl_3$) 15.02 (3D, br); 22.13 (t); 24.80 (t); 31.42 (t); 36.33 (t); 70.88 (d); 130.42 (d); 159.58 (d); 193.74(d).

MS: (CI^+) m/e (%abundance): 160 (M^+,100); 158 (6); 142 (17); 130 (5); 124 (6); 115 (6); 112 (10); 102 (19); 100 (7); 98 (9).

HRMS: (CI^+) Calculated for M^+ $C_9H_{14}O_2D_3$ 160.1414; Found 160.1427

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