PREPARATION OF ^{2}H- AND ^{13}C-LABELLED PRECURSORS OF 2-HYDROXY-1,3-BUTADIENE

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SUMMARY

2-exo-Vinylbicyclo[2.2.1]hept-5-en-2-ols, specifically labelled with ^{2}H at C-3 and in the vinyl group were prepared from bicyclo[2.2.1]hept-5-en-2-one in several steps. [4-^{13}C]Oct-1-en-3-one was prepared in five steps from $^{13}CO_2$. These compounds serve as precursors for the preparation of specifically labelled neutral and ionized 2-hydroxy-1,3-butadienes.

Key words: [4-^{13}C]oct-1-en-3-one, 2-exo-vinylbicyclo[2.2.1]hept-5-en-2-ols, ^{2}H-labelled.

INTRODUCTION

2-Hydroxy-1,3-butadiene [1] is an unstable enol that shows a peculiar loss of a methyl group following electron-impact ionization [2]. In order to explain the mechanism of this mass spectral fragmentation we needed to identify via specific ^{2}H and ^{13}C labelling the hydrogen and carbon atoms in the methyl eliminated. The $[CH_2{=}CH{-}C(OH){=}CH_2]^{+\cdot}$ ion can be generated by the retro-Diels-Alder fragmentation of 2-exo-vinylbicyclo[2.2.1]hept-5-en-2-ol , 1 ,[3],

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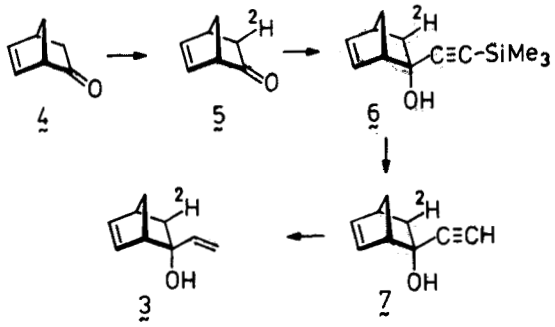
by the McLafferty rearrangement of terminal enones [2], e.g. oct-1-en-3-one, 2, or from substituted cyclohexenols [4]. For our purposes we have chosen to synthesize labelled analogues of the former two precursors.

SYNTHESIS

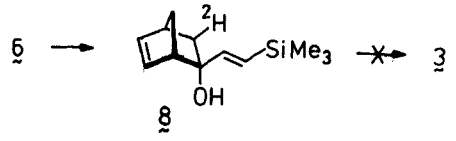
[exo-3-^{2}H]-2-exo-Vinylbicyclo[2.2.1]hept-5-en-2-ol (3), a precursor of [(E)-1-^{2}H]-2-hydroxy-1,3-butadiene, was prepared from bicyclo[2.2.1]hept-5-en-2-one (4) [5] (Scheme 1).



Scheme 1

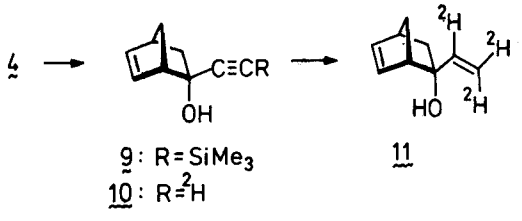
The exchange of the enolizable hydrogen atoms in 4 proceeded cleanly to give the singly deuterated ketone 5 which was treated with lithium trimethylsilylacetylide [6] to afford the protected alcohol 6. Desilylation [7] followed by hydride reduction [8] of the triple bond in 7 furnished the labelled alcohol 3. An alternative reaction sequence, consisting of reducing the triple bond first, encountered difficulties, since the vinyl silane 8 (Scheme 2) could not be desilylated under non-acidic conditions (e.g. n-Bu_4N^+ F^- in THF [9] or NaOH in

methanol [7]), while acidic treatment led to an untractable mixture of products, possibly arising by dehydration and skeletal rearrangements.



Scheme 2

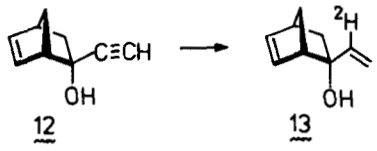
The derivatives labelled in the vinyl group were prepared by an analogous procedure (Scheme 3). Desilylation of the intermediate 9 with NaO^2H in CH_3O^2H afforded the labelled alcohol 10 10 which was reduced with lithium aluminum deuteride in THF. Quenching of the reaction mixture with deuterium oxide afforded the labelled alcohol 11 in which the labile hydroxylic deuterium was equilibrated with methanol to obtain the OH-form.



Scheme 3

Although the reduction of propargylic alcohols with lithium aluminum deuteride was reported to lead to non-specific deuterium introduction into the vinyl

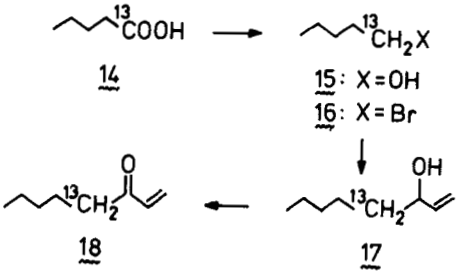
group [8], we have discovered that the reduction of 12 (Scheme 4) with $LiAl^2H_4$, followed by protic work-up, gave predominantly the labelled alcohol 13 (89%), accompanied by minor isotopomers containing the label in terminal positions (8% (E)-2-^{2}H and 3% (Z)-2-^{2}H).



12 13

Scheme 4

Introduction of ^{13}C label into 1 turned out to be troublesome, since the possible precursors, e.g. bicyclo[2.2.1]hept-5-en-2-ol-2-carboxaldehyde, are unstable and undergo rearrangements and ring opening [11]. We have therefore turned our attention to oct-1-en-3-one which was eventually prepared in the labelled form by the reaction sequence shown in Scheme 5.



14 18 17

Scheme 5

[1-^{13}C] Pentanoic acid (14), prepared from n-butyllithium and $^{13}CO_2$ by a modified Elbert protocol [12], was reduced to [1-^{13}C]pentanol (15) which was converted [13] to [1-^{13}C]1-bromopentane (16). The Grignard reagent prepared from 16 was allowed to react with acrolein to give alcohol 17 accompanied by [4-^{13}C]-octanal, a product of 1,4-addition. Octenol 17 was smoothly oxidized with active manganese dioxide [14] to the target enone 18.

Octenone 18 was found to be rather sensitive to polymerization. For instance, when unstabilized it did not survive three days' shipping via air mail. It can be stored for months at -20°C, or it can be conveniently stabilized with 0.3% of acetic acid, as described for 1-buten-3-one [15], and stored at 0°C.

EXPERIMENTAL

Methods. The NMR spectra were measured on a Varian XL-200 spectrometer (200.058, 50.309 and 30.71 MHz for ^{1}H, ^{13}C and ^{2}H, respectively, FT mode). The ^{1}H- and ^{13}C-NMR spectra were measured in deuteriochloroform at 22 °C and referenced to tetramethylsilane as internal standard. The ^{1}H-decoupled ^{2}H-NMR spectra were measured in unlocked mode in chloroform and referenced to the signal of deuteriochloroform (δ 7.26). The mass spectra were measured on a Jeol D-100 double-focusing spectrometer (75 eV, 300 μA, 3 kV) coupled to a gas chromatograph (column SE-30, 3% on Chromosorb W, 2.5 m/ 3 mm i.d.). Thin-layer chromatography (TLC) was performed on Silufol plates (Kavalier, Czechoslovakia), detection with a solution of potassium permanganate in 50% aqueous acetic acid.

Preparations. "Usual work-up" means drying the solution, filterring off the drying agent and distilling off the solvent through a 15 cm Vigreux column.

[3-exo-^{2}H]Bicyclo[2.2.1]hept-5-en-2-one (5). Ketone 4 (1.08 g, 10 mmol) [5] in dry THF (10 ml) was added to a solution of sodium deuteroxide (30 mg) and triethylbenzylammonium chloride (50 mg) in deuterium oxide (10 ml). The reaction flask was flushed with argon and the heterogeneous mixture was stirred at 20°C for 100 h. Then it was neutralized with solid CO_2, diluted with pentane (10 ml),

the water layer was separated and extracted twice with pentane (10 ml). Work-up followed by distillation in vacuo yielded 840 mg (78%) of oily 5 which crystallized upon standing at 0°C, m.p. 20-22 °C. Deuterium content (from the 11 eV mass spectrum): 4.4% $^2H_2$, 86.2% $^2H_1$, 9.4% $^2H_0$.

[3-exo-^{2}H]-2-exo-Vinylbicyclo[2.2.1]hept-5-en-2-ol (3). Ketone 5 (300 mg, 2.9 mmol) in THF (5 ml) was added at -78°C under argon to a solution of lithium trimethylsilylacetylide [6] (5 mmol) in THF (10 ml). After 30 min at -78°C and 1 h at 0°C the reaction was quenched with water and worked up. Crude 6 (490 mg, 86%) was dissolved in methanol (5 ml) and added at 0°C under argon to a solution of 0.1M-NaOH in methanol [7]. After 20 min stirring the product 7 (single spot by TLC, elution with pentane-ether, 3:2) was extracted with pentane, worked up and purified by distillation in vacuo to give 260 mg (70% based on 5) of a semi-crystalline material. ^{1}H-NMR: δ 6.44 (dd, 1H), 6.11 (dd, 1H), 3.11 (m, 1H), 2.92 (m, 1H), 2.55 (s, 1H), 1.80 (s, 1H), 1.77 (d, J=9.8 Hz, 1H), 1.63 (dm, 1H), 1.33 (dt, J_d = 3.6 Hz, J_t = 2.0 Hz, 1H); Alcohol 7 (240 mg, 1.8 mmol) in THF (5 ml) was added to a slurry of lithium aluminum hydride (76 mg, 2 mmol) in THF (5 ml) and the mixture was refluxed under argon for 6 h. The excessive hydride was decomposed with a saturated aqueous solution of sodium sulfate, and the THF solution was worked up. Distillation in vacuo (120 °C/ 12 Torr) yielded 180 mg (74%) of 3; Deuterium content: 4% $^2H_2$, 87% $^2H_1$, 9% $^2H_0$. ^{2}H-NMR: δ 2.03. Mass spectrum (m/z, rel. intensity): 137(3), 136(0.4), 118(1), 109(1), 108(2), 92(5), 80(4), 71(15), 66(100), 61(4), 55(10), 45(14), 43(16), 39(11).

[3-exo-^{2}H]-2-exo-((E)-2-Trimethylsilylvinyl)bicyclo[2.2.1]hept-5-en-2-ol (8). Alcohol 6 (150 mg, 0.7 mmol) was reduced with lithium aluminum hydride (50 mg, 1.3 mmol) in THF (5 ml) as described for 7. Work-up afforded 120 mg (79%) of 8, m.p. 51°C . ^{1}H-NMR: δ 6.31 ,5.95(AB,J=18.8. Hz), 1.14(dt, 1H), 0.09(s,9H). Mass spectrum (m/z, rel. intensity): 209(3), 128(55), 118(25), 117(35), 75(100), 73(30), 66(82), 59(12).

Refluxing 8 with four to ten-fold molar excess of tetrabutylammonium fluoride in THF for 24 h led to complete recovery of the starting compound.

2-exo-([1,2,2-$^2H_3$]Vinyl)bicyclo[2.2.1]hept-5-en-2-ol (11). A solution of 9 (500 mg, 2.4 mmol) prepared from 4 and lithium trimethylsilylacetylide [3,6], in CH_3O^2H (3 ml) was added at 0°C to 0.1 M-NaO^2H in CH_3O^2H (5 ml). After stirring for 20 min the reaction mixture was worked up and 2-exo-([2-^2H]ethynyl)-bicyclo[2.2.1]hept-5-en-2-ol (10) was isolated by distillation in vacuo. Yield 220 mg (67%). ^{1}H-NMR: δ 6.44 (dd, 1H), 6.11 (dd, 1H), 3.11 (m, 1H), 2.92 (m, 1H), 2.35 (dd, 1H), 1.78 (s, 1H), 1.77 (dm, 1H), 1.63 (dm, 1H), 1.34 (dd, 1H). Alcohol 10 (200 mg, 1.5 mmol) in THF (5 ml) was added to a slurry of lithium aluminum deuteride (80 mg, 1.9 mmol) in THF (5 ml), and the mixture was refluxed under argon for 6 h. The deuteride was decomposed with deuterium oxide (1 ml), the resulting gel was precipitated with sodium sulfate, and the mixture was worked up. The crude product was dissolved in methanol (2 ml), allowed to stand for 1 h, and the solvent was slowly distilled off in vacuo at 0°C. Vacuum distillation afforded 140 mg (68%) of 11 which gave a single spot by TLC (elution with pentane-ether 2:1) and a single peak by GC. ^{1}H-NMR: δ 6.49 (ddd, 1H), 6.21 (dddm, 1H), 2.91 (m, 1H), 2.77 (m, 1H), 2.04 (dd, 1H), 1.56 (m, 1H), 1.16(ddd, 1H). ^{2}H-NMR: δ 6.18, 5.33, 5.11. ^{13}C-NMR: δ 140.63 (d), 133.14 (d), 71.30 (s), 54.43 (d), 48.75 (t), 43.43 (t), 43.13 (d). Mass spectrum (m/z, rel.intensity): 139(4), 120(1), 107(1), 96(5), 81(4), 80(4), 79(4), 73(12), 66(100), 58(5), 43(6), 42(5), 41(7), 40(6), 39(11). Deuterium content: 87.5% $^2H_3$, 12.5% $^2H_2$.

2-exo-([1-^2H]Vinyl)bicyclo[2.2.1]hept-5-en-2-ol (13). Alcohol 12 (250 mg, 1.9 mmol) [3] was reduced with lithium aluminum deuteride (80 mg, 1.9 mmol) in THF (5 ml), reflux for 6 h. The mixture was diluted with ether (10 ml), quenched with a saturated solution of sodium sulfate and worked up. Distillation in vacuo yielded 220 mg (86%) of pure (by TLC and GC) 13. ^{2}H-NMR: δ 6.17 (89%), 5.33 (8%), 5.09 (3%). ^{13}C-NMR: δ 140.93, 133.63, 112.10, 71.63, 53.82, 49.14, 43.73, 43.52. Mass spectrum (m/z, rel. intensity): 137(3), 119(1), 109(2), 108(1), 96(2), 95(2), 94(5), 81(3), 80(4), 79(6), 71(16), 66(100), 56(11), 43 (5), 40(8), 39(13). Deuterium content: 96% $^2H_1$, 4% $^2H_0$.

[1-^{13}C]Pentanoic acid (14). $^{13}CO_2$ (from 5 mmol of $Ba^{13}CO_3$, 85% ^{13}C) was condensed with dry pentane (15 ml) at -196°C in a flask attached to a vacuum line [12].

The flask was warmed to ca. -100 °C in a bath containing a mixture of methanol, ethanol and liquid nitrogen, pressurized to 133 kPa with argon, and a solution of butyllithium in a mixture of pentane and hexane (0.2 M), precooled to -78 °C, was slowly injected below the surface [12]. The mixture was stirred at -100 °C for additional 20 min and then at -78°C for 1 h. Then it was warmed to 0 °C and poured to 0.5 M-NaOH (50 ml). The water solution was extracted with ether (4 x 20 ml), acidified with concentrated hydrochloric acid to pH 0, and acid 14 was extracted with ether. The extract was worked up and the residue was distilled in vacuo to give 430 mg (84%) of 14, b.p. 80-90 °C/ 15 Torr, n_D^{20} 1.409.

[1-^{13}C]Pentanol (15). Acid 14 (410 mg, 4 mmol) in ether (10 ml) was added to a slurry of lithium aluminum hydride (300 mg, 8 mmol) in ether (20 ml). The mixture was refluxed for 6 h and then worked up. Distillation in vacuo yielded 330 mg (93%) of 15, b.p. 70-80 °C/ 50 Torr, n_D^{20} 1.4115.

[1-^{13}C]-1-Bromopentane (16). Phosphorus tribromide (320 mg, 1.2 mmol) in pentane (2 ml) was added dropwise at -40 °C to a stirred solution of 15 (270 mg, 3 mmol) and pyridine (75 mg) in pentane (2 ml). The mixture was stirred at -20 °C for 1 h, and the products were distilled off at atmospheric pressure [13]. The obtained solution of 16 was diluted with pentane (10 ml), washed with 5%HCl, 10% HNO_3, water, 5% $KHCO_3$ and worked up. The residue was distilled to give 350 mg (76%) of 16, b.p. 50-60 °C/ 50 Torr, n_D^{20} 1.4465. ^{1}H-NMR: δ 3.40 (dt, $J(^{13}C-{}^1H)$= 150.5 Hz, 2H), 1.84 (m, 2H), 1.37 (m, 2H), 1.26 (m, 2H), 0.88 (t, 3H).

[4-^{13}C]Oct-1-en-3-ol (17). Bromide 16 (330 mg, 2.2 mmol) in ether (5 ml) was added dropwise to crushed magnesium shavings (100 mg, 4.1 matom) in refluxing ether (3 ml). The mixture was refluxed for 1 h, then cooled , decanted, and the solution was transferred with a syringe to another flask. To the cooled solution of the Grignard reagent it was slowly added a solution of freshly distilled acrolein (140 mg) in ether (3 ml). The mixture was stirred at 0 °C for 1 h, quenched with ammonium chloride solution and worked up. The crude product was distilled in vacuo to give 380 mg (64%) of 17 contaminated with ca. 10%

(by GC) of [4-^{13}C]octanal. Alcohol 17 was purified by column chromatography (silica gel, elution with pentane-ether, 2:1) to give 260 mg of a pure product, n_D^{20} 1.4370. ^{13}C-NMR : δ 37.00 (t) (enriched).

[4-^{13}C]Oct-1- en-3-one (18). Alcohol 17 (240 mg, 1.9 mmol) in pentane (3 ml) was stirred with freshly prepared [14] manganese dioxide (1 g) under argon. After 4 h the oxidation was complete (TLC analysis, pentane-ether, 2:1), the mixture was diluted with pentane (15 ml), filterred and worked up. Short-path distillation at 60 °C/ 10 Torr afforded 210 mg (89%) of pure 18 of intense mushroom smell. n_D^{20} 1.445. ^{1}H-NMR : δ 6.36 (ddd, J = 17.4, 10.0, $^2J(^{13}C-^1H)$ = 1.2 Hz, 1H), 6.20 (dd, J = 17.4, 2.0 Hz, 1H), 5.80 (dd, J = 10.0, 2.0 Hz, 1H), 2.58 (dt, $^1J(^{13}C-^1H)$ = 124.7 Hz, J_t = 7.7 Hz, 2H), 1.61 (m, 2H), 1.28 (m, 4H), 0.87 (t, 3H). ^{13}C-NMR : δ 185.7 (d, $^1J(^{13}C-^{13}C)$ = 38 Hz), 136.58 (d, $^2J(^{13}C-^{13}C)$ = 13.8 Hz), 127.83, 39.61 (enriched), 34.07, 31.42, 23.68 (d, $^1J(^{13}C-^{13}C)$ = 35 Hz), 13.91. Mass spectrum (m/z, rel. intensity): 98(10), 97(8), 84(9), 83(5), 71(78), 70(22), 55(100), 44(13), 43(20), 42(9), 31(13), 27(30).

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