EFFICIENT SYNTHESES OF (±) [2-$^2H_2$]MEVALONOLACTONE AND (±) [2-$^2H_2$]HOMOMEVALONOLACTONE

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SUMMARY

Efficient syntheses of (±) [2-$^2H_2$]mevalonolactone and (±) [2-$^2H_2$]homomevalonolactone involving condensations of lithiotrimethylsilyl [2-$^2H_2$]acetate with appropriate 3-oxo-alcohols are described. Regiospecificity of the label was established by NMR spectroscopy.

Key words: Trimethylsilyl [2-$^2H_3$]acetate, (±) [2-$^2H_2$]mevalonolactone, (±) [2-$^2H_2$]homomevalonolactone, juvenile hormone, NMR spectroscopy.

Recently, we have described a short radiosynthesis of (±) [2-^{14}C]mevalonolactone (1). In recent years, substrates labelled with stable isotopes are finding increasing applications in biosynthetic studies (2). In this communication, efficient syntheses of deuterium labelled mevalonolactone (1) and its homolog (2) are described. Excellent retention of the labels shows that although labels are present in labile position (α to carbonyl group), no significant isotopic exchange took place under the conditions of the synthesis. The regiospecificity of the label was established by NMR spectroscopy.

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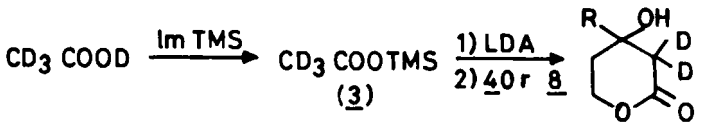
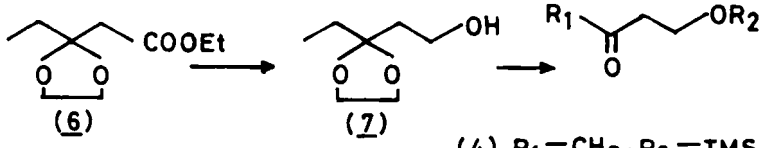


(1) R = CH_3
(2) R = Et



(4) $R_1 = CH_3$; R_2 = TMS
(5) $R_1 = C_2H_5$; R_2 = H
(8) $R_1 = C_2H_5$; R_2 = TMS

(±) [2-$^2H_2$]Mevalonolactone (1)

Trimethylsilyl[2-$^2H_3$]acetate (3) was prepared in 97% yield by the action of [$^2H_4$]acetic acid and N-TMS imidazole. Lithio enolate of 3 generated by the action of LDA at -78°, was condensed with 1-trimethylsilyloxy-3-butanone (4) as described earlier (3). [2-$^2H_2$]MVA (1) was obtained in 77% yield. When compared with the ^1H NMR spectrum of normal MVA, spectrum of (1) did not show any difference in the relative intensities and the chemical shifts of the signals except the disappearance of the signal at δ 2.61, which corresponds to protons at position 2 of normal MVA. This established the regiospecificity of the labelling; retention of ^2H was more than 95%.

(±) [2-$^2H_2$]Homomevalonolactone (2)

It has been established that the ethyl branches of homoterpenoid juvenile hormones have their origin in homomevalonate (HMVA) (4). Labelled HMVA's are therefore required for metabolic studies in insects. (±) [2-$^2H_2$] HMVA (2) has been synthesised by the condensation of 3-oxo-pentan-1-ol (5) with 3.

The key intermediate, namely 3-oxo-pentan-1-ol (5) was prepared in high yield by the following route. 3,3-Ethylenedioxypentan-1-ol (7) was prepared by the reduction of ethyl-3,3-ethylenedioxypentanoate (6) using lithium aluminium hydride (5). Deketalisation of 7 could not be carried out by usual methods since the resultant compound, 3-oxo-pentan-1-ol (5) is labile due to presence of a hydroxyl group β to the carbonyl function. Also, 5 is water soluble and its isolation from aqueous phase presents practical difficulties while dealing with small scale experiments using isotopically labelled compounds. Use of acid supported on SiO_2 have been found to be excellent reagent for such deketalisation (6). Of the several reagents tried, p-toluenesulphonic acid supported on SiO_2 gel was found to be the most convenient for deketalisation of 7; compound 5 was obtained in 93% yield. The product thus obtained was transformed into 1-trimethylsilyloxy-3-pentanone (8) using N-TMS-imidazole. The condensation of 8 with lithiotrimethylsilyl[2-$^2H_2$] acetate was carried out at -78°. The reaction mixture was worked up by careful acidification with aqueous hydrochloric acid to pH 3 which removed the TMS protections of the hydroxyl and carboxyl groups and also affected lactonisation. Thus (±) [2-$^2H_2$]homomevalonolactone (2) was obtained in 70% yield.

In the ^{1}H-NMR spectrum of 2, signals for protons at 2-position were absent indicating complete deuteration at this position. This shows that no deuterium exchange took place during the course of the reaction. In the ^{13}C-NMR spectrum of [2-$^2H_2$]HMVA, the signals for the carbon at 2-position were very weak. This is attributed to the loss of NOE due to replacement of ^{2}H for ^{1}H and also extensive ^{2}H-^{13}C splittings.

Using appropriately labelled starting materials, other labelled MVA and its analogs can be prepared by this synthetic procedure.

EXPERIMENTAL

Trimethylsilyl [$^2H_3$]-acetate (3)

A mixture of [$^2H_4$]acetic acid (distilled, bp 114°, 1.8 g, 28 mmol), and N-TMS-imidazole (4.2 g, 30 mmol) (7) was stirred at 5° for 10 min. and

then allowed to attain room temperature. Trimethylsilyl [2-$^2H_3$]acetate was distilled directly from the reaction mixture. Yield: 3.7 g (97%), b.p. 102-4°. 60 MHz-PMR (CCl_4): δ, 0.18 [s, -Si $(CH_3)_3$].

(±) [2-$^2H_2$]Mevalonolactone (1)

To a stirred and cooled (-78°) solution of lithium diisopropylamide (4 mmol) in THF (30 ml), trimethylsilyl [2-$^2H_3$]acetate (3), (540 mg, 5 mmol) was added. After stirring for 1.5 hr. 1-trimethylsilyloxy-3-butanone (4, 640 mg, 4 mmol) (3) in THF (5 ml) was added. After 2 hr., the reaction mixture was diluted with ether and worked up as described earlier (3). The product was purified by column chromatography. GLC (OV-17, 5%, 136°): homogeneous. Yield: 400 mg (77%). 60 MHz-PMR ($CDCl_3$): δ, 1.35 (s, 3H), 1.90 (m, 2H), 4.08 (s, exchangeable with D_2O) and 4.5 (m, 2H).

3-Oxo-pentan-1-ol (5):

An aqueous solution of p-toluenesulphonic acid (0.9 ml, 10%) was added to a stirred suspension of SiO_2 (9 g, NCL Poona, 70-200 mesh) in dichloromethane. After the disappearance of aqueous phase (5 min) due to adsorption on silica gel, 3,3-ethylenedioxypentan-1-ol (7) (2.0 gm), was added dropwise and stirring was continued. On completion of the reaction (3 hr. monitored by disappearance of signals at 958 & 913 cm^{-1} in the IR spectrum) the reaction mixture along with SiO_2 was poured on the top of a dry column of SiO_2 (9 gm) and eluted with dichloromethane (200 ml). Ethylene glycol is retained in the column while 3-oxo-pentan-1-ol (5) (1.3 gm, 93%) was obtained on removal of the solvent from the eluant at room temperature. It was pure enough (NMR) for its use in the next stage. 60 MHz-PMR ($CDCl_3$): δ, 1.06 (t, 3H, J = 7 Hz, $\underline{CH_3}CH_2$), 2.33-2.8 (m, 4H, -$\underline{CH_2}$-CO-$\underline{CH_2}$-), 3.46 (s, 1H, -$\underline{OH}$, exchangeable with D_2O), 3.9 (t, 2H, -$\underline{CH_2}$ -OH); IR (film) υ max: 3448 (-OH); 1715 (C=O) cm^{-1}.

1-(Trimethylsilyloxy)-3-pentanone (8):

To a vigorously stirred suspension of (5) (1.1 gm, 12 mmol) in dry n-pentane (50 ml), N-TMS-imidazole (2.2 gm, 15 mmol) was added dropwise

(5 min) at 25° under dry conditions. An immediate precipitation of imidazole was observed. After stirring for 2 hr. the precipitate was separated by decantation. Removal of solvent at room temperature under dry conditions gave colourless oil which was distilled under reduced pressure; yield 1.8 gm (85%); b.p. 104°/55 mm.

(±) [2-$^2H_2$]Homomevalonolactone (2)

Compound 2 was prepared in (70%) yield by the method described above from 5 mmol (540 mg) of trimethylsilyl [2-$^2H_3$] acetate (3) and 5 mmol (870 mg) of 1-trimethylsilyloxy-3-pentanone (8). The crude product on distillation gave (2) as a colourless thick liquid (b.p. 128°/0.1 mm; 462 mg) 500 MHz-PMR($CDCl_3$): (8) δ ,0.9 (t, 3H, CH_3-), 1.54(m, 2H, -CH_2-CH_3), 1.82(m, 2H, -CH_2-CH_2-O), 3.44 (s, 1H, OH), 4.29 and 4.54 (two m, 2H, -CH_2-CH_2-O). 125.8 MHz-^{13}CMR ($CDCl_3$) : δ , 7.18 (CH_3-CH_2-), 33.82 and 34.99 (CH_3-CH_2- and -CH_2-CH_2-O-), 42.8 (ill-defined m, -CD_2-COO-), 65.9 (-CH_2-CH_2-O-], 70.5 (3- -$\overset{OH}{C}$-) 171 (- COO-)

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8. Assignments of signals in the PMR spectra are based on COSY-45 measurements. Carbon signals in the CMR spectra were assigned on the basis of SFORD experiments. Spectra were taken on Brucker AM-500 MHz FT-NMR Spectrometer. We are grateful to 500 MHz FT-NMR National Facility, TIFR, for the spectral determinations.