Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXIV, No. 12

SYNTHESIS OF MEVALONOLACTONE DOUBLE LABELLED WITH CARBON ^{13}C AT POSITIONS C-2 AND C-4

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SUMMARY

The total synthesis of the title compound from pyruvic aldehyde dimethyl acetal and ethyl [2-^{13}C]acetate is reported.

Key words: Mevalonolactone, Labelling with carbon ^{13}C.

INTRODUCTION

Stereospecifically labelled mevalonolactones with stable and radiolabelled isotopes have been essential in the elucidation of biosynthetic mechanisms. (3RS)-[2,4-$^{13}C_2$]mevalonolactone was needed to determine the distribution of label in 3-acetyldeoxynivalenol[1]. There is no reported synthesis of (3RS)-[2,4-$^{13}C_2$]mevalonolactone and the known synthesis[2-7] of mevalonolactones cannot be applied for this specific labelling purpose. We have used a high yield synthetic strategy (scheme 1) which was easy to perform.

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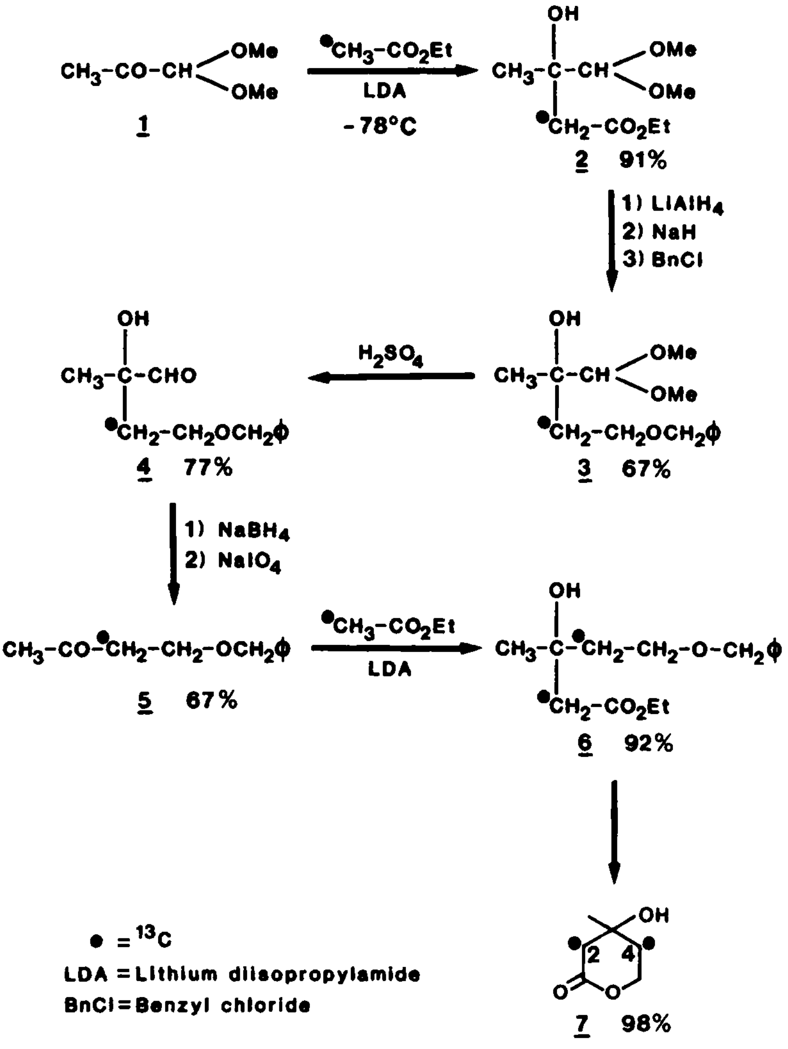
0362-4803/87/121461-07$05.00

Received January 3,1987
Revised March 18, 1987

RESULTS AND DISCUSSION



SCHEME 1

The first reaction involving the labelling with ^{13}C was the condensation of pyruvic aldehyde dimethylacetal (1) with ethyl [2-^{13}C]acetate in the presence of lithium-diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C. After the usual work up, purification by flash chromatography gave ethyl [2-^{13}C]-3-hydroxy-3-methyl-4,4-dimethoxybutanoate (2) with 91% yield. The ^{1}H-NMR spectrum of compound 2 showed a doublet assigned to $^{13}C\underline{H}_2$ -CO_2Et at 2.50 ppm with a coupling constant J_{CH} = 128 Hz. Reduction of compound 2 by an excess of lithium aluminum hydride ($LiAlH_4$) in THF, followed by benzylation of the resulting primary alcohol with NaH-benzylchloride in N,N-dimethylformamide (DMF) gave [2-^{13}C]-1-benzyloxy-3-hydroxy-3-methyl-4,4-dimethoxybutane (3) with 67% overall yield after flash chromatography. The ^{1}H-NMR spectrum of 3 indicated a doublet of triplet at 1.95 ppm assigned to $^{13}C\underline{H}_2$-CH_2O with coupling constants J_{CH} = 128 Hz and J_{HH} = 7 Hz. [2-^{13}C]-1-benzyloxy-3-hydroxy-3-methyl-4-oxobutane (4) isolated from acidic hydrolysis of 3 in dioxane (77% yield), was reduced with sodium borohydride ($NaBH_4$), and the corresponding diol was oxidized with sodium periodate ($NaIO_4$) to yield [2-^{13}C]-1-benzyloxy-3-oxobutane (5) (overall yield: 67%). The structure of 5 was in good agreement with its ^{1}H NMR spectrum: δ(ppm) = 2.10 (d), J_{CCCH} = 1.5 Hz, 3H, (CH_3); 2.75 (dt), J_{HH} = 6Hz, J_{CH} = 128 Hz, 2H, ($^{13}CH_2$-CO). Condensation of compound 5 with ethyl [2-^{13}C]acetate , LDA, at -78°C in THF similarly to the first reaction resulted in the formation of ethyl [2,4-$^{13}C_2$]-3-hydroxy-3-methyl-5-benzyloxypentanoate (6) (yield: 92%) which underwent cyclization upon palladium catalytic hydrogenation in hydrochloric methanol to give [2,4-$^{13}C_2$]mevalonolactone (7) (yield: 98%).

EXPERIMENTAL

Instrumentation

Infrared (IR) spectra were obtained on a Perkin Elmer 683 spectrophotometer. Proton magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian T-60 spectrometer using internal tetramethylsilane. Mass spectra (MS) were taken on a HP5980A mass spectrometer at 70 e.V.

Materials

Tetrahydrofuran was freshly distilled over lithium aluminum hydride just prior to use. N,N-Dimethylformamide and diisopropylamine were distilled on calcium chloride. Ethyl [2-

^{13}C]acetate was purchased from Merck Sharp and Dohme Isotopes. Flash chromatography was carried out using silica gel (200-400 mesh) purchased from B.D.H. Chemicals.

Ethyl [2-^{13}C]3-Hydroxy-3-methyl-4,4-dimethoxybutanoate ($\underline{2}$)

In a round bottom flask fitted with an argon inlet 22.69 mmol of diisopropylamine were dissolved in 50 mL of THF. After cooling this mixture to -78°C with a Dry Ice acetone bath, 22.69 mmol of n-butyllithium were added slowly. The reaction mixture was magnetically stirred at this temperature for 15 min. Then ethyl [2-^{13}C]acetate (20.62 mmol) in 2 mL of THF was added dropwise, and the stirring at -78°C was continued for 30 min more. Finally, 20.62 mmol of pyruvic aldehyde dimethylacetal in 3 mL of THF were added dropwise, while the temperature was kept unchanged. The reaction mixture was quenched one hour later with 10 mL of saturated aqueous solution of ammonium chloride. After evaporation of the organic solvent, the crude product was extracted with ether, washed with water, dried over magnesium sulfate, filtered and evaporated to dryness. Flash chromatography on silica gel with ethyl acetate : hexane (1:2) gave 4.29 g of ester $\underline{2}$ (91% yield).

^{1}H NMR (CDCl$_3$) δ (ppm)= 1.25 (t),$^3J_{HH}$ = 7Hz, (CH_2-$C\underline{H}_3$); 1.30 (d), J_{CCCH} = 4Hz, (CH_3), total 6H; 2.5 (d), J_{CH} = 128 Hz, 2H, ($^{13}C\underline{H}_2$ - CO_2); 3.50 (s), 6H, $(OCH_3)_2$; 4.20 (q), $^3J_{HH}$ = 7Hz, (CH_3 - $C\underline{H}_2$); 4.25 (d), J_{CCCH} = 4HZ, $C\underline{H}(OMe)_2$, total 3H.

IR ($CHCl_3$) νmax = 3500, 1725 cm^{-1}

MS m/e = 132 [M-CH(OMe)$_2$]$^+$

Trimethylsilyl derivative: m/e = 204 [M - CH(OMe)$_2$]$^+$; 232 [M - CH$_3$ -MeOH]$^+$; 234 [M - C_2H_5O]$^+$

[2-^{13}C]-1-Benzyloxy-3-hydroxy-3-methyl-4,4 - dimethoxybutane ($\underline{3}$)

Under argon atmosphere, 20.28 mmol of $LiAlH_4$ were poured into a round bottom flask containing 50 mL of THF. The resulting mixture was stirred magnetically for 15 min at 0°C. Then 4.20 g (20.28 mmol) of ester $\underline{2}$ in 10 mL of THF were added slowly by means of an equalizer pressure dropping funnel. After 1 h of stirring at 0°C, the reaction was quenched with 4 mL of methanol. After evaporation to dryness under vacuum, the crude product was extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness. The resulting alcohol (2.28 g) was then dissolved in 12 mL of DMF, cooled to 0°C and 607 mg of 60% NaH were added under argon atmosphere. The stirring was continued for 15 min at 0°C, then 15.19 mmol of benzyl chloride in 4 mL of DMF were added. The reaction mixture was stirred at 0°C for 3 h, then overnight at room temperature. The reaction was quenched with addition of 466 mg of sodium methoxide and stirring for 30 min at room temperature. After extraction with ether, washing with brine and drying over magnesium sulfate, the crude product was purified by flash chromatography with ethyl acetate : hexane (1:1). Overall yield: 67%.

^1H NMR ($CDCl_3$) δ (ppm)= 1.20 (d), J_{CCCH} = 4Hz, 3H, (CH_3); 1.95 (dt), J_{HH} = 7Hz, J_{CH} = 128Hz, 2H, ($^{13}CH_2$); 3.5 (s), 6H, $(OCH_3)_2$; 3.70 (dt), J_{HH} = 7Hz, J_{CCH} = 5Hz, 2H, (CH_2O); 4.00 (d), J_{CCCH} = 3Hz, 1H, ($C\underline{H}$ $(OMe)_2$); 4.50 (s), 2H, ($C\underline{H_2}$ ϕ); 7.25(s), 5H, (ϕ).

IR($CHCl_3$) νmax = 3500, 700 cm^{-1}

MS m/e = 180 $[M - CH (OMe)_2]^+$; 134 $[M - CH_2OCH_2\phi]^+$

Trimethylsilyl derivative m/e = 252 $[M - CH (OMe)_2]^+$; 134 $[M - SiMe_3 -CH_2OCH_2\phi]^+$.

[2-^{13}C]-1-Benzyloxy-3-hydroxy-3-methyl-4-oxobutane (4)

Compound 3 (3.0 g) (11,76 mmol) was stirred at room temperature in a round bottom flask containing 100 mL of dioxane and 100 mL of 1N H_2SO_4. The hydrolysis was complete 7 h later. After neutralization with 1N NaOH, the crude product was submitted to the usual work up, then purified by flash chromatography with ethyl acetate : hexane (1:2). Yield: 77%.

^1H NMR ($CDCl_3$) δ (ppm)= 1.25 (d), J_{CCCH} = 4Hz, 3H, (CH_3); 1.95 (dt), J_{HH} =6Hz, J_{CH} = 128 Hz, 2H, ($^{13}CH_2$); 3.60 (dt), J_{HH} = 6Hz, J_{CCH} = 3 Hz, 2H, ($^{13}CH_2$ -$C\underline{H_2}O$), collapsed with OH peak; 4.40(s), 2H, ($CH_2\phi$); 7.30 (s) 5H,(ϕ); 9.55(s), 1H, (CHO).

IR ($CHCl_3$) ν max = 3500, 1720, 700 cm^{-1}

MS m/e = 180 $[M - CHO]^+$; 191 $[M - H_2O]^+$; 162 $[M - CHO - H_2O]^+$

Trimethylsilyl derivative m/e = 252 $[M - CHO]^+$; 145 $[M -{}^{13}CH_2CH_2OCH_2\,\phi]^+$.

[2-^{13}C]-1-Benzyloxy-3-oxobutane (5)

Aldehyde 4 (1.90 g) was reduced with 515 mg of $NaBH_4$ in 20 mL of methanol at 0°C. The reduction was complete within 15 minutes. The resulting compound was extracted with ethyl acetate, washed with brine, dried over magnesium sulfate and evaporated to dryness after filtration. The crude product was then dissolved in 30 mL of acetone, and 2.98 g of

$NaIO_4$ were added, followed by 2 mL of water. The reaction mixture was stirred at room temperature for 2 h. The white precipitate was filtered and the filtrate evaporated to dryness. Flash chromatography with ethyl acetate : hexane (1:2) gave pure compound 5. Overall yield: 67%.

^1H NMR ($CDCl_3$) δ(ppm)= 2.10 (d), J_{CCCH} = 1.5Hz, 3H, (CH_3); 2.75 (dt), J_{HH} = 6Hz, J_{CH} = 128Hz, 2H, ($^{13}CH_2$); 3.70 (dt), J_{HH} = 6Hz, J_{CCH} = 3Hz, 2H, ($^{13}CH_2$ - $C\underline{H_2}O$); 4.50(s), 2H, ($CH_2\phi$); 7.35(s), 5H, (ϕ).

IR($CHCl_3$) ν_{max} = 1720, 700 cm^{-1}.

MS m/e = 179 $[M]^+$; 121 $[\phi CH_2OCH_2]^+$;107 $[OCH_2\phi]^+$.

Ethyl [2,4-$^{13}C_2$]3-Hydroxy-3-methyl-5-benzyloxypentanoate (6)

Under argon atmosphere, 11.23 mmol of diisopropylamine were added dropwise into a round bottom flask containing 35 mL of THF. After cooling this mixture to -78°C with a Dry Ice-acetone bath, 11.23 mmol of n-butyllithium were added dropwise by means of an equalizer pressure dropping funnel, while the magnetic stirring was continued for 15 minutes at -78°C. Then 1 g of ethyl[2-^{13}C]acetate was introduced. The stirring at -78°C was continued for twenty-five minutes more and 5.43 mmol of compound 5 in 5 mL of THF were added. The resulting mixture were stirred during forty-five additionnal minutes (the temperature was kept unchanged) then quenched with 2 mL of water. After the usual work up, the crude product was purified by flash chromatography using ethyl acetate : hexane (1:3). Yield: 92%.

^1H NMR ($CDCl_3$) δ(ppm)= 1.25 (t), J_{HH} = 7Hz, (CH_2-$C\underline{H_3}$); 1.30 (m), (CH_3), total 6H; 1.90 (ddt), J_{CH} = 127Hz, J_{HH} = 7Hz, J_{CCCH} = 3 Hz, 2H, ($^{13}C\underline{H_2}$-CH_2O); 2.55 (dm), J_{CH} = 128 Hz, 2H, ($^{13}CH_2$-CO_2); 3.85 (m), 2H, ($C\underline{H_2}$ -$OCH_2\phi$); 4.15 (q), J_{HH} = 7 Hz, 2H, ($C\underline{H_2}$ - CH_3); 4.50 (s), 2H, ($OCH_2\phi$); 7.25 (s), 5H, (ϕ).

IR ($CHCl_3$) ν_{max} = 3500, 1720, 700 cm^{-1}

MS m/e=253$[M-CH_3]^+$; 223$[M-C_2H_5O]^+$;
180 $[M-^{13}CH_2CO_2C_2H_5]^+$; 132 $[M - \phi CH_2OCH_2{}^{13}CH_2]^+$.

Trimethylsilyl derivative m/e = 204 $[M - \phi CH_2OCH_2{}^{13}CH_2]^+$

[2,4-^{13}C]Mevalonolactone (7)

4.80 mmol of ester 6 were dissolved in 50 mL of methanol and 0.60 mL of 1N HCl was added, followed by 280 mg of 10% palladium on carbon catalyst. The mixture with hydrogen bubbling through it was magnetically stirred at room temperature for 2 h. After filtration through a Celite column, the filtrate was neutralized with ion exchange resin 1X8 (OH^-). After evaporation to dryness, the crude product was purified by flash chromatography with ethyl acetate : hexane (2:1). Yield: 98%.

^1H NMR ($CDCl_3$) δ(ppm)= 1.40 (t), J_{CCCH} = 4Hz, 3H, (CH_3); 1.90 (dm), J_{CH} = 128Hz, 2H, (4-H); 2.55 (dm), J_{CH} = 128 Hz, 2H, (2-H); 3.00 (s), 1H, (OH); 4.40 (m), 2H, (5-H).

IR ($CHCl_3$) νmax = 3450, 1740 cm^{-1}

MS Trimethylsilyl derivative m/e = 189 $[M - CH_3]^+$

ACKNOWLEDGEMENTS

We thank Agriculture Canada and National Science and Engineering Research Council of Canada for support of this work.

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