SYNTHESIS OF MEVALONOLACTONE-2,3-$^{13}C_2$

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SUMMARY

The synthesis of mevalonolactone with ^{13}C-labels at positions 2 and 3 is reported. Hydrolysis of methyl 3-hydroxy-3-methyl-5,5-dimethoxy-valerate-2,3-$^{13}C_2$ to the aldehydo acid followed by reduction with sodium borohydride yielded the title compound. The material is useful as a substrate in biosynthetic studies using ^{13}C-NMR as an analytical tool.

Key Words: Mevalonolactone-2,3-$^{13}C_2$, ^{13}C-NMR, Biosynthesis

INTRODUCTION

Biosynthetic studies concerning the origin of various fungal metabolites required the synthesis of mevalonolactone specifically labeled with ^{13}C at positions 2 and 3. In an earlier communication we reported the synthesis of mevalonolactone-3,4-$^{13}C_2$. [1] We now describe the transformation of a key intermediate (3) from that process into mevalonolactone-2,3-$^{13}C_2$ (1).

The previously described [1] synthesis of the acetal ester (3) entailed acylation of acetylene by acetyl-1-^{13}C chloride as catalyzed by aluminum chloride followed by treatment of the chloroenone intermediate with sodium methoxide in methanol to afford 1,1-dimethoxy-3-butanone-2-^{13}C (2). Rathke condensation of 2 with methyl lithioacetate-2-^{13}C at -78°

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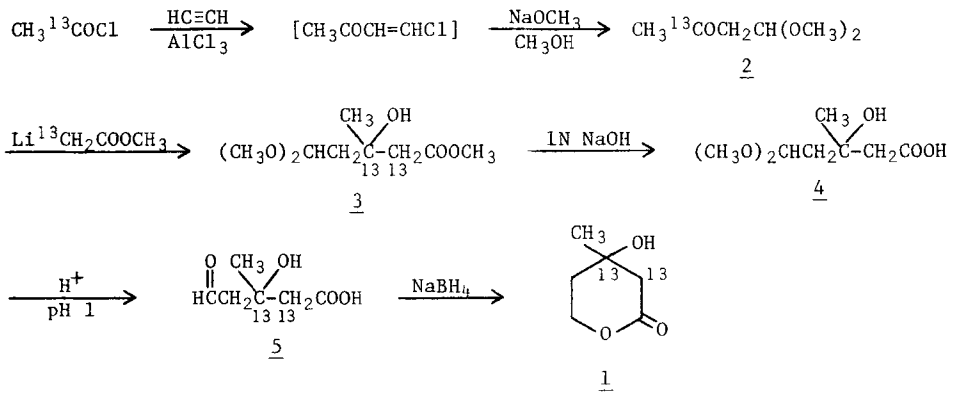
yielded the β-hydroxy ester acetal (3). Attempts to directly hydrolyze the acetal in acidic media with subsequent reduction of the liberated aldehyde and concommitant ring closure to mevalonolactone were unsuccessful. Gas chromatographic analysis indicated a multiplicity of products, while NMR examination suggested β-elimination of the tertiary hydroxyl group was a primary course of reaction.

The route eventually employed for conversion of 3 to mevalonolactone was based on the 3-step procedure of Shunk et al., [2] culminating in a 51% yield of 1 without isolation of intermediates. Saponification of the ester group in 1N sodium hydroxide followed by acidification to pH 1 afforded the acetal acid (4). Continued exposure of 4 to the acidic medium promoted hydrolysis of the acetal to produce the aldehydo acid (5). Reduction of the aldehyde with sodium borohydride yielded mevalonolactone-2,3-$^{13}C_2$ (1). Hydrogenation of 5 over platinum or rhodium catalysts failed to give the lactone. The ^{13}C-NMR spectrum of 1 showed doublets for the two adjacent enriched ^{13}C-atoms at 68.20 ppm (3-^{13}C) and 44.74 (2-^{13}C).



EXPERIMENTAL

Mevalonolactone-2,3-$^{13}C_2$ (1)

A mixture of 1.10 g (5.2 mmole) of methyl 3-hydroxy-3-methyl-5,5-dimethoxyvalerate-2,3-$^{13}C_2$ (3) and 5.5 ml of 1N sodium hydroxide was stirred at ambient temperature for 45 minutes. The resulting solution

was cooled to 0-5° and the pH adjusted to 1 with 6N hydrochloric acid. The mixture was allowed to warm to room temperature and was stirred for another 15 minutes. The temperature was again lowered to 0-5° and the pH adjusted to 7.5 by addition of saturated sodium bicarbonate solution. To this chilled solution of the aldehydo acid (5) was added dropwise 200 mg (5.3 mmole) of sodium borohydride in 3 ml of 1N sodium hydroxide. Stirring was continued at room temperature for another 1.5 hours, whereupon the solution was chilled to 0-5° and acidified (pH 1-2) with 6N hydrochloric acid. The solution was washed twice with 5-ml portions of pentane and evaporated in vacuo (below 45°) to leave a semisolid residue. The residue was extracted twice with 50-ml portions of acetone and the extract dried over anhydrous potassium carbonate. After filtration the solvent was removed in vacuo to leave 353 mg (51%) of mevalonolactone-2,3-$^{13}C_2$ (1) as an oil whose gas chromatographic behavior was identical to authentic mevalonolactone. The NMR and IR spectra were very similar to the natural material except for differences caused by ^{13}C substitution. The ^{13}C-NMR showed only 2-enriched carbons as doublets with the 3-^{13}C occurring at 68.20 ppm and the 2-^{13}C at 44.74 ppm with a coupling constant of 36.6 herz.

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