# SYNTHESIS OF (±) [2-$^{14}$C]MEVALONOLACTONE IN ONE STEP

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## SUMMARY

Condensation between 1-trimethylsilyloxy-3-butanone and trimethylsilyl [2-$^{14}$C]acetate gave (±) [2-$^{14}$C]mevalonolactone in one step.

Key words: (±) [2-$^{14}$C]mevalonolactone, trimethylsilyl [2-$^{14}$C]acetate, 1-trimethylsilyloxy-3-butanone.

(±)[2-$^{14}$C]Mevalonolactone (MVA) is the most widely used substrate in the biosynthesis of terpenoids and steroids. Conventionally, it has been prepared by the Reformatsky reaction between methyl [2-$^{14}$C]bromoacetate and 1-acetoxy-3-butanone (1). More recently, an elegant synthesis of MVA has been described by Ellison and Bhatnagar (2) in which ethyl lithioacetate is condensed with 1-acetoxy-3-butanone. Alkaline hydrolysis of the pentanoate obtained by either of the above methods give MVA. Recently we have described a synthesis of MVA which involves the condensation between 1-trimethylsilyloxy-3-butanone (2) and trimethylsilyl acetate (3). Utilisation of this method to the synthesis of (±)[2-$^{14}$C]MVA (3) is described in this communication (4). MVA is obtained directly in this procedure since acidic work up of the reaction cleaves the TMS protection obviating an additional step of deprotection used in other syntheses. Another advantage of this radiosynthesis is that labelled trimethylsilyl acetate is more easily prepared than labelled ethyl acetate or methyl bromoacetate used in other methods.

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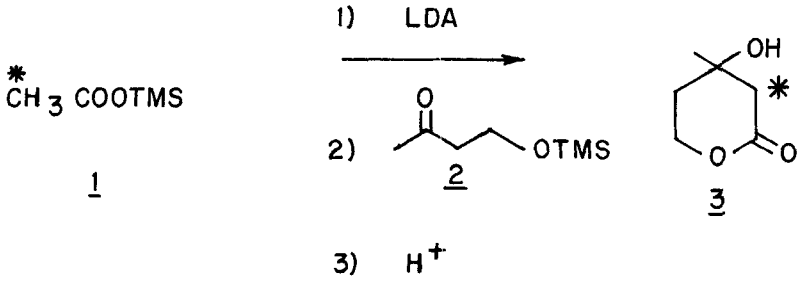


Trimethylsilyl [2-$^{14}$C]acetate (1) was prepared by the action of [2-$^{14}$C]acetic acid and N-trimethylsilylimidazole in excellent chemical and radiochemical yields. It was lithiated at -78° by the action of lithium diisopropylamide (LDA). The lithioacetate was condensed with 1-trimethylsilyloxy-3-butanone (2) (3) at -78°. The reaction mixture was acidified to pH 3 which resulted in hydrolysis of TMS groups and [2-$^{14}$C]MVA (3) was obtained in high chemical and radiochemical yields.

## EXPERIMENTAL

Radioactivity of labelled compounds were measured by liquid scintillation spectrometry (Beckman liquid scintillation counter, models LS 100). Identities of the labelled compounds were established by comparison with authentic samples (3).

Trimethylsilyl [2-$^{14}$C]acetate (1): N-Trimethylsilylimidazole (5) (260 mg, 1.86 mmol) was added dropwise to [2-$^{14}$C]acetic acid (108 mg, 1.80 mmol. 1.13 mCi/mmol) which was cooled to 5°C. An instant reaction took place with the separation of imidazole. Trimethylsilyl [2-$^{14}$C]acetate was collected in a receiver cooled to -78° by vacuum transfer technique (0.03 mm). Yield, 233 mg (98.3%); sp. activity, 1.04 mCi/mmol; b.p., 102°, lit. b.p., (6), 102.5-103°.

(±) [2-$^{14}$C]Mevalonolactone (3): To a stirred solution (30 ml, freshly dried THF) of lithium diisopropylamide (2.0 mmol; prepared by the action of n-butyllithium and diisopropylamine) at -78°C, trimethylsilyl [2-$^{14}$C]acetate (208 mg, 1.57 mmol, 1.04 mCi/mmol) was added. After stirring for 1.5 hr, 1-trimethylsilyloxy-3-butanone (2) (303 mg, 1.89 mmol) was added and stirring continued. On completion of the reaction (2 hr) the mixture was diluted with ether (100 ml) and acidified with 6N HCl to pH 3. The aqueous portion was saturated with $NH_4Cl$ and extracted with a mixture (1:10) of $CHCl_3$/ether (5 x 50 ml). The combined organic layers were dried over anhydrous $Na_2SO_4$. Evaporation of the solvent gave a residue (204 mg) which was purified by flash column chromatography (silica gel, National Chemical Laboratory, Poona, 10 gm). Elution with benzene removed the excess of reactants; (±) [2-$^{14}$C]MVA could be recovered from the column by elution with ethyl acetate. Removal of the solvent gave (±) [2-$^{14}$C]MVA as a colourless liquid. Yield, 169 mg (82.5%); b.p., 107°/0.02 mm; 0.93 mCi/mmol). In the rechromatography, EtOAc eluent which contained (±) [2-$^{14}$C]MVA, accounted for 94-97% of the initial radioactivity. The radiochemical purity as estimated by TLC (silica gel G, SISCO Laboratory, Bombay; solvent : benzene 3, EtOAc 7) was $>$ 95%. The overall recovery of radioactivity based on [2-$^{14}$C]acetic acid was 66.7%. The chemical identity was confirmed by direct comparison (IR, NMR, GLC) with an authentic sample of MVA (3).

## REFERENCES

1. Cornforth J.W. and Cornforth R.H., in "Natural Substances Formed Biologically from Mevalonic Acid", Ed. T.W. Goodwin, Biochemical Society Symposium no. 29, Academic Press, New York. (1970) pp. 1.

2. Ellison R.A. and Bhatnagar, P.K. - Synthesis 719 (1974).

3. Banerji A. and Kalena G.P. - Syn. Commun. 12, 225 (1982).

4. Preliminary communication: Banerji A. and Kalena G.P. - Proceedings of the Annual Convention of Chemists, Madras, 1981, Abstract no. Bio - 21.

5. Birkofer L., Richter P. and Ritter A. - Chem. Ber. 93, 8204 (1960).

6. Schuyten H.A., Weaver J.W. and Heid, J.D. - J. Amer. Chem. Soc. 69, 2110 (1947).