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NEW ROUTE TO (3RS) (5R) (5-^{2}H)- AND (3RS) (5S) (5-^{2}H)-MEVALONOLACTONES

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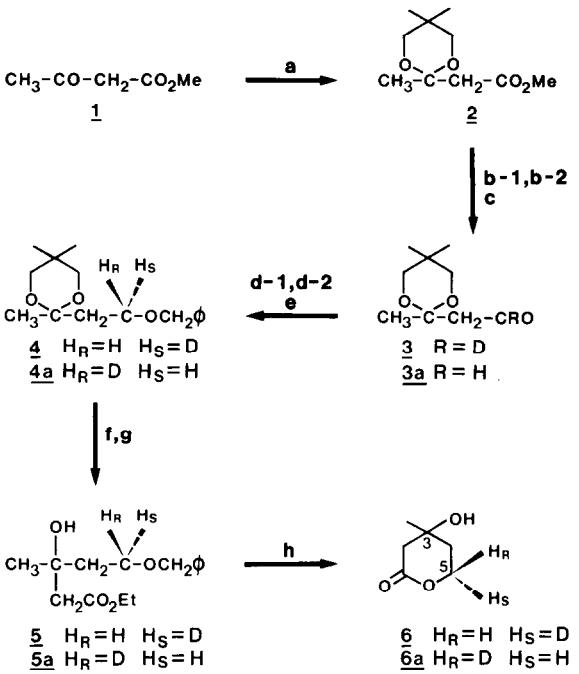
SUMMARY: The synthesis of mevalonolactone stereospecifically labeled at carbon 5 is described combining chemical reactions with an enzymatic reduction step.

Mevalonolactone is the key precursor for the large family of terpenoid natural products. We have been particularly interested in the enantiospecific synthesis of deuterated mevalonolactones at carbon C-5. Indeed, this would correspond to position 3 of oxygenated trichothecenes (i.e. 3-acetyldeoxynivalenol) and this will allow verification of the stereochemistry of this oxygenation[1]. There is only one basic procedure known in the literature[2], but it is not applicable to the production of large quantities ($\sim$900 mg) of stereospecifically C-5 labeled mevalonate, since the overall yield is low (3.1%) and the reactions are difficult to repeat. Indeed, the key intermediate, 3-methyl (1-^{3}H) but-3-enal is very volatile and is also unstable since it readily isomerizes to the conjugated α-β unsaturated aldehyde. We report in this paper a new synthesis of these compounds using very stable intermediates, simple routes and higher yield (35%). This synthesis is amenable to the production of large quantities of (3RS) (5R) (5-^{2}H)-, (3RS) (5S) (5-^{2}H)- and (3RS) (5RS) (5-^{2}H$_2$)-mevalonic acids in one week, from commercially available methyl acetoacetate.

The basic strategy developed involves enzymatic reduction (horse liver alcohol dehydrogenase in the presence of NAD$^+$ and ethanol-d_6 or unlabeled ethanol) of the appropriately labeled aldehydes. The precise synthetic sequence is detailed in Fig. 1. A methylene chloride solution of methylacetoacetate was treated with trimethylchlorosilane, 2,2-dimethylpropane-1,3-diol at reflux temperature overnight[3]. Usual work up followed neutralization with $NaHCO_3$ solution. Compound 2 was isolated and purified by flash chromatography. The yield of pure 2 was 98%. The ester 2 was reduced either with $LiAlH_4$ or $LiAlD_4$ and oxidized with pyridinium dichromate in CH_2Cl_2 to give the aldehyde 3a (or 3) in an overall yield of 63%. The intermediate 3 was reduced enzymatically with horse liver alcohol dehydrogenase, nicotinamide adenine dinucleotide and ethyl alcohol (or ethanol-d_6 for 3-a) in 0.05M potassium phosphate buffer (pH 8.8)[4]. The resulting product was treated with NaH/benzylchloride in N,N-dimethyl formamide to give compound 4 or 4a. (overall yield: 65%). Derivative 4 or 4a was first deprotected to the ketone with methanolic hydrogen chloride (98% yield), then the ketone condensed with ethyl acetate/lithium diisopropylamide at -78°C in THF to give ester 5 (or 5a) (93% yield) which underwent cyclization upon palladium catalytic hydrogenation in methanolic hydrogen chloride to afford final (3RS) (5S) (5-^{2}H)- (6) or (3RS) (5R) (5-^{2}H)-mevalonolactones (6a). The stereospecificity of enzymatic reduction of aldehydes by

horse liver alcohol dehydrogenase is known[4] to be enantiotopically specific for the re-face of the carbonyl group in 3 or 3a. Since there is retention of configuration at this carbon for the subsequent steps we obtain the mevalonolactones described. Compound 6 (as well as 6a) which is an equal mixture of the 3R and 3S forms, is a mixture of diastereomers as a result of isotopic substitution. The ^{1}H-NMR and ^{2}H-NMR of 6 and 6a are therefore identical. In the ^{1}H-NMR two groups of peaks are detected, one corresponding to 5-H_{axial} (at 4.312 ppm) and one to 5-$H_{equatorial}$ (at 4.571 ppm). The ^{2}H-NMR of 6 or 6a obviously shows two single peaks at the same positions as the ^{1}H-NMR.



Synthesis of stereospecifically labeled mevalonates at position 5. The reactions corresponding to a-h are: a: trimethylchlorosilane, 2,2-dimethylpropane-1,3-diol, CH_2Cl_2, reflux. b-1: $LiAlD_4$, THF, 0°C. b-2: $LiAlH_4$, THF, 0°C. c: Pyridinium dichromate, CH_2Cl_2 reflux; d-1: Horse liver alcohol dehydrogenase, NAD^+, 0.05M phosphate buffer, pH 8.8, ethanol. d-2: horse liver alcohol dehydrogenase, NAD^+, 0.05M phosphate buffer, pH 8.8, ethanol-d_6. e: NaH, benzyl chloride, N,N-dimethylformamide, room temperature; f: HCl, MeOH; g: ethyl acetate, lithium diisopropylamide; h: H_2, Pd, HCl, MeOH.

FIGURE 1.

Acknowledgments

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