Fifty years of the synthesis of labelled mevalonic acid

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This article reviews developments in the synthesis of isotopically-labelled samples of mevalonic acid for use in studies of terpenoid and steroid biosynthesis.

Keywords: mevalonic acid, mevalonate, carbon-13, carbon-14, deuterium, tritium, oxygen-18

The discovery[1,2] in 1956 that mevalonic acid **1**, was a major precursor of the C_5 isoprene unit which characterises the terpenoids and steroids, revolutionised this area of biosynthesis. The biosynthetic origin of the carbon atoms of cholesterol from acetate units had been established by that time and it was clear that each C_5 isoprene unit was derived from three acetate units with the loss of one carboxyl carbon. A search was then being made for potential C_6 intermediates that would generate the C_5 building block.

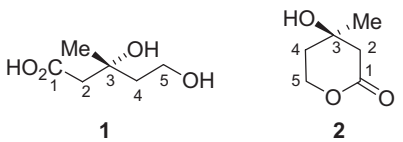
In 1956 an acetate-replacing factor which sustained the growth of a strain of *Lactobacillus acidophilus,* was obtained from dried distillers' yeast by a group working in the Merck laboratories in the USA. The structure of the compound as the δ-lactone **2** of 3,5-dihydroxy-3-methylvaleric acid **1** was established[3,4] on the basis of its IR spectrum, the formation of derivatives and a simple degradation. The original trivial name given to the compound was divalonic acid. This was changed to mevalonic acid and the lactone was renamed as mevalonolactone when the full paper[4] was published in 1957. A partial synthesis by the selective reduction of one of the ester groups of dimethyl 3-hydroxy-3-methylglutarate **3** confirmed the structure.

Fortuitously a research group in an adjacent Merck laboratory was studying the biosynthesis of cholesterol in rat liver homogenates. [2-^{14}C]Mevalonolactone, (±)-**2**, was synthesised by a Reformatski reaction using ethyl [2-^{14}C]-bromoacetate **4** and 4-acetoxybutan-2-one **5** and found to be a very effective precursor of cholesterol.[1,2] In 1957,[5-7] it was shown to be a precursor of squalene and within a few years mevalonolactone was established as a precursor of the C_5 isoprenoid building block, isopentenyl diphosphate **6** and many terpenoids including several fungal sesqui- and di-terpenoids (for reviews see refs 8 and 9). In biosynthetic studies mevalonolactone has been used interchangeably with mevalonic acid.

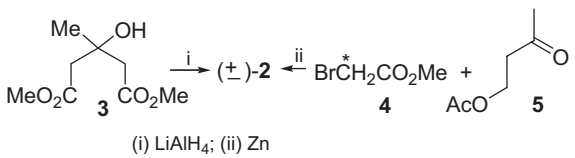
In 1956, mevalonolactone was independently isolated from the fungus *Aspergillus oryzae* as a growth factor for the Hiochi spoilage organism and named hiochic acid lactone. The structure which was originally proposed for this metabolite was incorrect. Its identity with mevalonolactone was established[10] in 1958.

In recent years an alternative biosynthetic pathway based on l-deoxy-D-xylulose and leading to isopentenyl diphosphate **6**, has been identified (for a review see ref. ll). Whereas the mevalonate pathway is the dominant pathway in mammals and fungi, the l-deoxy-D-xylulose pathway is more common in bacteria and in the chloroplasts of plants. Both pathways are found in other parts of plants.

Mevalonolactone is a chiral molecule. The absolute stereochemistry of the biologically-active (3*R*)-enantiomer was established by correlation[12] with quinic acid **7** of known absolute stereochemistry. The carboxyl group of quinic acid in a selectively protected derivative **8** was converted into a methyl group. After further degradation the 3(*S*)-(+)- enantiomer of the naturally-occurring mevalonolactone was obtained.



Scheme 1



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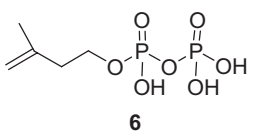
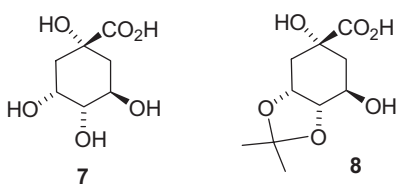


Scheme 3



Scheme 4

Inter-relationship[13] with (*R*)- and (*S*)-linalool correlated the absolute stereochemistry of the naturally-occurring mevalonic acid with that of these monoterpenes and also served to correct some earlier work on linalool. The double bonds of linalool **9** were hydroboronated to a triol **10** and its l:3-glycol was protected as a dioxane with acetaldehyde. Oxidation of the remaining hydroxyl group afforded a ketone. In the course of this work a novel way of cleaving a carbon chain adjacent to a ketone group was devised. Condensation of the methylene adjacent to the ketone group with methyl formate and sodium methoxide gave a hydroxymethylene ketone **11** which was oxidised with aqueous sodium periodate to afford the nor-acid. The protecting group was hydrolysed during the work-up. (3*R*)-(–)-Mevalonolactone **2** was obtained from (+)-linalool **6**. Biosynthetic studies[13] showed that only the 3(*R*)-mevalonolactone was biologically active as a substrate for mevalonate kinase from rat liver. The 3(*S*)-enantiomer was recovered unchanged.

Over the intervening 50 years, the synthetic chemistry of mevalonolactone has been dominated by a number of features. The isoprene unit is the biological building block for the terpenoids. A number of stages may be discerned in the

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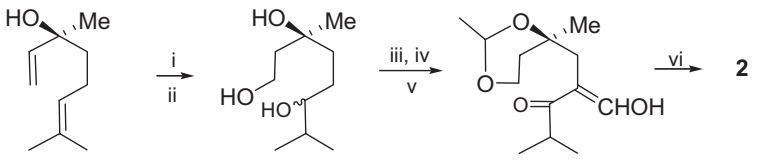


(i) B_2H_6; (ii) H_2O_2, OH^-; (iii) CH_3CHO, H^+; (iv) CrO_3, pyr; (v) HCO_2Et, NaOMe; (vi) $NaIO_4$.

Scheme 5

biosynthetic sequence from mevalonic acid to the terpenoids. Firstly there is the formation of the C_5 units and their stepwise oligomerisation to form the $(C_5)_n$ isoprenoid chains. Secondly there are the cyclisations of these to form the parent skeleta of the different families of terpenoids and finally there are the hydroxylations and other oxidations which lead to the individual terpenoids. The branched chain structure of the isoprenoid backbone and the carbocationic nature of the cyclisations, provides the potential for many skeletal and hydrogen rearrangements during a biosynthetic sequence. Consequently different carbon-labelled and stereospecifically deuteriated and tritiated mevalonates have been synthesised in order to unravel the course of these rearrangements and to identify the ultimate fate of the isoprenoid units. Furthermore the biosynthesis of mevalonic acid from 3-hydroxy-3-methylglutaryl co-enzyme A is the target for the widely used statin family of cholesterol biosynthesis inhibitors.

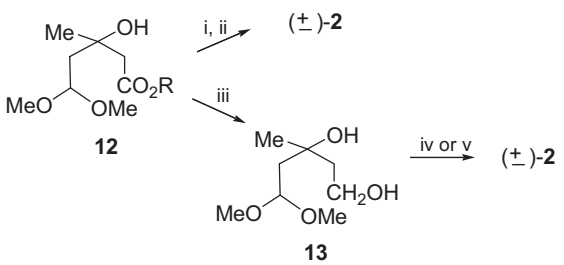
Although outside the scope of this review, the synthesis of mevalonolactone has attracted interest for another reason. The presence of a chiral tertiary alcohol in this relatively simple molecule has made the compound a target in order to validate novel asymmetric synthetic strategies. Recently mevalonolactone has been produced commercially as a cosmetic additive for skin conditioning.

Carbon-labelled mevalonates

The presence of a β-hydroxycarbonyl moiety in mevalonolactone is a retrosynthetic marker for a condensation reaction between a C_2 carbanion source and a C_4 unit containing a carbonyl group. The early syntheses were based on a Reformatski reaction between a C_4 unit such as 4-acetoxybutan-2-one, 4-benzyloxybutan-2-one, 4-chlorobutan-2-one or 4,4-dimethoxybutan-2-one and methyl or ethyl bromoacetate.[14-17] Subsequently more efficient condensation reactions have been developed based on the lithium carbanion derived from methyl or ethyl acetate or the dilithium anion derived from acetic acid.[18] Full experimental details for this procedure are given in ref.19.

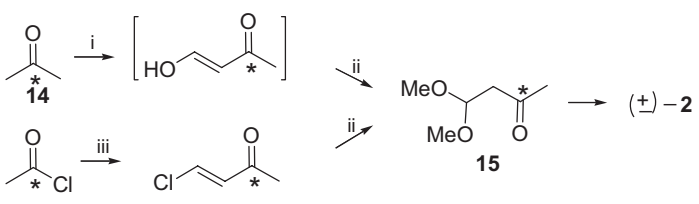
A useful feature of the synthesis using 4,4-dimethoxybutan-2-one is that the two 'arms' of mevalonolactone (C-l and C-2, C-4 and C-5) can be interchanged. The acetal **12** (R = Me) may be hydrolysed and reduced to afford the C-5 of mevalonolactone or the ester may be reduced to a primary alcohol **13** and then the acetal may be hydrolysed and subjected to a mild oxidation to generate the lactone carbonyl (C-l). The flexibility of these strategies is revealed by their use for the synthesis of mevalonolactone labelled on each of the carbons using 1-or 2-labelled acetic acid as the source of the label. Some examples are as follows.

[2-^{13}C]Mevalonolactone has been prepared by the condensation of the lithium dianion of [2-^{13}C]acetic acid with 4-benzyloxybutan-2-one.[19] [4-^{13}C]Mevalonolactone was prepared[20] by the condensation of the lithium enolate of ethyl [2-^{13}C]acetate with 4,4-dimethoxybutan-2-one. The ester was reduced with lithium aluminium hydride and the resultant primary alcohol was acetylated. Hydrolysis and oxidation of the acetal with performic acid gave the labelled mevalonate. A similar procedure has been used[2l] for the synthesis of [4,5-$^{13}C_2$]mevalonolactone from [1,2-$^{13}C_2$]-acetate. The procedure was adapted[22] for the synthesis of [3,4-$^{13}C_2$]mevalonate. 4,4-Dimethoxy-[2-^{13}C]butan-2-one **15** was prepared by the reaction of [2-^{13}C]acetone **14** with methyl formate in the presence of sodium methoxide. This was followed by treatment with methanolic hydrogen chloride. The labelled butanone **15** was then reacted with the lithium enolate of ethyl [2-^{13}C]acetate as described previously to give the [3,4-$^{l3}C_2$]mevalonate. An alternative preparation of 4,4-dimethoxy-[2-^{13}C]butan-2-one **15** involved[23] the reaction of [l-^{13}C]acetyl chloride **16** with acetylene in the presence of aluminium trichloride. The unstable 4-chloro-[2-^{13}C]but-3-en-2-one **17** was converted directly into the dimethoxyacetal with methanolic sodium methoxide. Mevalonolactone has also been synthesised[24] by an internal Reformatski reaction which used 4-bromoacetoxybutan-2-one prepared from bromoacetyl bromide and 4-hydroxybutan-2-one.



(i) H^+; (ii) $NaBH_4$; (iii) $LiAlH_4$; (iv) Br_2, H_2O; (v) H_2O_2, AcOH

Scheme 6



(i) HCO_2Me, NaOMe; (ii) HCl, MeOH; (iii) HC≡CH, $AlCl_3$

Scheme 7

In the preparation[16] of [3',4-$^{l3}C_2$]mevalonolactone from [2-^{13}C]acetic acid, [2-^{13}C]acetyl chloride **18** was converted into diketene **19** with triethylamine. Reduction of the diketene with lithium aluminium hydride gave 4-hydroxy-[l,3-$^{13}C_2$] butan-2-one **20**. In this particular synthesis, the mevalonolactone was prepared by treatment of the acetate of **20** with ketene in the presence of boron trifluoride. The initial product of the addition of ketene to the carbonyl group of 4-acetoxybutan-2-one was a β-lactone which was easily hydrolysed to mevalonic acid.

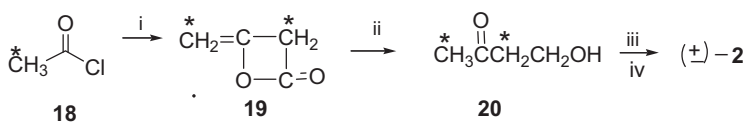
[2,4-$^{13}C_2$]Mevalonolactone was prepared[25] by condensation of ethyl [2-^{13}C]acetate and 3,3-dimethoxypropan-2-one (pyruvic aldehyde dimethylacetal) **21**. Reduction of the ester and benzylation of the primary alcohol to form **22** was followed by hydrolysis of the acetal. Cleavage of the resultant α-hydroxyaldehyde via the corresponding l,2-diol gave 4-benzyloxy-[3-^{13}C]butan-2-one **23**. Condensation with a second molecule of ethyl [2-^{13}C]acetate and hydrolysis gave the required [2,4-$^{13}C_2$]mevalonolactone.

The 1,3,5-trioxoadamantyl group has been used[26] as a protected carboxylic acid in syntheses which parallel those using 4,4-dimethoxybutan-2-one. This avoids the separate hydrolysis and oxidation steps involved with the acetal. In this synthesis trioxoadamantylacetyl chloride **24** was condensed with the lithium anion of bis(trimethylsilyl)malonate **25** to give a methyl ketone **26**. This ketone was reacted with lithium [$^{14}C_2$]acetylide to give an ethynyl alcohol **27** from which [4,5-$^{14}C_2$]mevalonolactone was obtained by hydroboration and further reduction to give **28**. Hydrolysis of the trioxoadamantyl protecting group then gave the labelled mevalonolactone.

The 3-hydroxy-3-methyl moiety of mevalonolactone is also a retrosynthetic marker for a Grignard reaction. A number of deuteriated and tritiated as well as carbon-labelled mevalonates have been prepared by strategies based on this dissection. 3-Hydroxy-3-methylglutaric anhydride **31** has been prepared[27,28] labelled at either C-3 or on the methyl group by a Grignard reaction between 1- or 2-labelled ethyl acetate and allyl magnesium bromide. Ozonolysis of the double bonds in the Grignard adduct **29** and oxidation gave 3-hydroxy-3-methylglutaric acid **30**. Cyclisation of the dicarboxylic acid to form the anhydride **31** has been problematic. The best results have been obtained[28] with dicyclohexylcarbodiimide. The anhydride was then reduced with sodium borohydride to give the labelled mevalonolactone. Alternatively reduction of the ozonolysis product to a triol **32** and controlled oxidation with chromium trioxide in acetic acid[29] or silver carbonate gave mevalonolactone.[30] This procedure has been used to prepare both [3'-^{13}C] and [3'-$^{2}H_3$]mevalonates.

Although it has not been used in the preparation of labelled material, the desymmetrisation of dimethyl 3-hydroxy-3-methylglutarate **3** by the enantiospecific hydrolysis of one of the ester groups with pig liver esterase, has been reported.[31,32] Reduction of the carboxylic acid with borane:dimethylsulfide gave the 3*S*-(+)-mevalonolactone whilst reduction of the ester with lithium borohydride gave 3*R*-(–)-mevalonolactone.

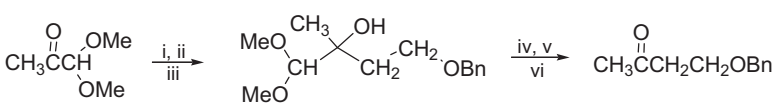
Oxygen-labelled mevalonolactone The fate of the oxygen atoms of mevalonic acid in isoprenoid biosynthesis has been examined by oxygen-18 labelling. The methods that were used to introduce the label were modifications of those that were used for carbon-labelling. [3-^{18}O]Mevalonolactone was prepared[33] by the acid-catalysed exchange of the ketonic oxygen of 4-acetoxybutan-2-one with [^{18}O]water. The isotopic label was retained in a Reformatski reaction with ethyl bromoacetate to give [3-^{18}O]mevalonolactone. [5-^{18}O] Mevalonolactone was prepared[34] by the acid-catalysed hydrolysis of the acetal **12** (R = Me) in [^{18}O]water followed by reduction of the [^{18}O]aldehyde with sodium borohydride.



18 **19** **20**

(i) Et_3N; (ii) $LiAlH_4$; (iii) CH_2=C=O, $BF_3.Et_2O$; (iv) OH^-.

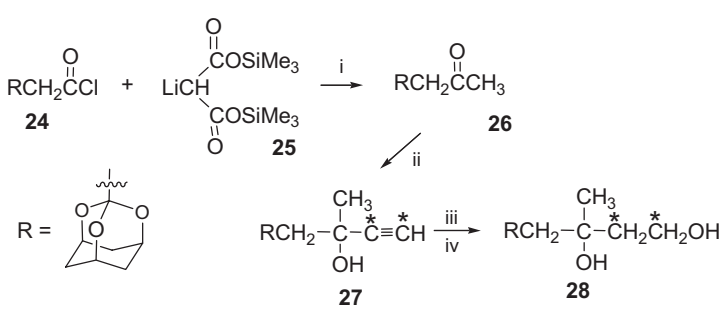
Scheme 8



21 **22** **23**

(i) CH_3CO_2Et, BuLi; (ii) $LiBH_4$; (iii) BnCl, NaH; (iv) H^+; (v) $NaBH_4$; (vi) $NaIO_4$

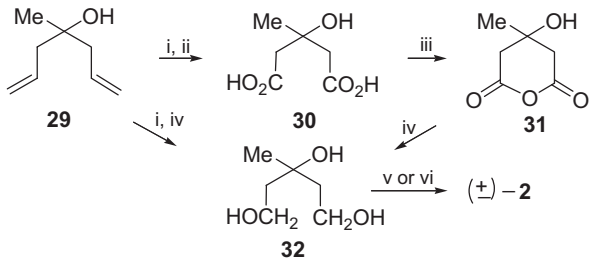
Scheme 9



24 **25** **26** **27** **28**

(i) H^+, (ii) $Li\overset{*}{C}\equiv\overset{*}{C}H$; (iii) 9BBN; (iv) H_2O_2, OH^-.

Scheme 10



29 30 31 32

(i) O_3; (ii) H_2O_2, AcOH; (iii) AcOH or DCC; (iv) $LiAlH_4$; (v) CrO_3, AcOH; (vi) Ag_2CO_3.

Scheme 11

Deuteriated and tritiated mevalonates

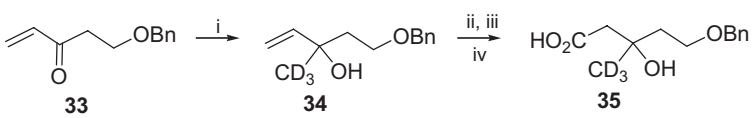
Many of the methods that are described above have been modified to afford non-stereospecifically deuteriated or tritiated mevalonates bearing labels at C-2, C-4, C-5 and on the methyl group by using deuteriated or tritiated acetate or reducing agents as the source of the label.[35-37]

A route based on a Grignard reaction has been used[38] in a synthesis of [3'-$^2H_3$]mevalonolactone starting from pent-4-en-l-ol. The primary alcohol was protected as its benzyl ether. Oxidation of the allylic C-3 position with selenium dioxide and chromium trioxide gave a ketone **33**. A Grignard reaction with [$^2H_3$]methyl magnesium iodide was used to introduce the trideuteriomethyl group to give **34**. Hydroboration of the alkene gave a primary alcohol which was oxidised to the corresponding carboxylic acid **35**. Hydrogenolysis of the benzyl protecting group allowed lactonisation to occur.

Perdeuteriated [$^2H_9$]mevalonolactone has been prepared[39] from 3,4-dimethoxypropiophenone in which oxidation of the reactive aromatic ring provided the carboxylic acid. The enolisable hydrogens of 3,4-dimethoxypropiophenone were exchanged and the deuteriated product was then condensed with a [$^2H_2$]phosphonate in a Wadsworth–Emmons reaction to give the unsaturated ester **36**. Reduction of the ester with lithium aluminium deuteride gave the corresponding [$^2H_8$]allylic alcohol. This was epoxidised with *t*-butyl hydroperoxide and vanadylacetylacetonate and the epoxide **37** was reduced with lithium aluminium deuteride to create a tertiary alcohol. The hydroxyl groups were protected as acetates and the carboxyl group of mevalonic acid was generated by oxidative cleavage of the aromatic ring with ruthenium trichloride and sodium periodate. Hydrolysis of the acetate afforded [$^2H_9$]mevalonolactone. An enantioselective version of this synthesis has been developed[40] to give 3*R*-[$^2H_9$]mevalonolactone by using a Sharpless asymmetric epoxidation [*t*-butylhydroperoxide, L-(+)-diisopropyl tartrate and titanium isopropoxide] to generate the chiral epoxide. Another synthesis of 3*R*-[$^2H_9$]mevalonolactone made use[41] of the asymmetry of a readily available derivative **39** of glucose to act as a chiral template to induce asymmetric epoxidation. Methyl [$^2H_7$]senecioate **38** was prepared by a Wittig reaction between [$^2H_6$]acetone and ethoxycarbonyl[^2H]methylene (triphenyl)phosphorane and condensed with the C-3 ketone derived from diacetoneglucose to give **40**. The isopropylidene glycol on the sugar differentiated between the faces of the alkene in the spirolactone **40**. This directed the nucleophilic addition of hydrogen peroxide to give one epimer of an epoxide. Reduction with lithium aluminium deuteride gave a triol **41**. Hydrolysis of the isopropylidene groups and oxidative degradation of the chiral template with sodium periodate gave 3*R*-[$^2H_9$]mevalonolactone.

Another example of the preparation of a multiply-labelled mevalonate was the synthesis[42] of [4-$^2H_2$,3-^{13}C] mevalonolactone which was required for studies on hydrogen rearrangements in biosynthesis. [2-^{13}C]Acetone was converted into 4,4-dimethoxy[2-^{13}C]butan-2-one by condensation with methyl formate as described previously. The addition of the lithium carbanion derived from ethyl acetate yielded ethyl 5,5-dimethoxy-3-hydroxy-3-methyl-[3-^{13}C]pentanoate **12** (R = Et). The hydrogen atoms at C-2 were exchanged with deuterium using methanol-O-D and sodium methoxide. The ester was then reduced to form a primary alcohol which becomes C-5 of mevalonolactone whilst the acetal was hydrolysed to expose the aldehyde. Oxidation of the aldehyde to a carboxyl group gave the required mevalonolactone. The deuterium label which was introduced at C-2 in the pentanoate, then appears at C-4 in the mevalonate.

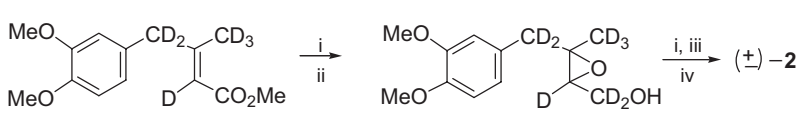
The hydrogen atoms at C-2, C-4 and C-5 of mevalonic acid participate in many biosynthetic reactions. Stereospecifically labelled mevalonates have been required in order to establish the stereochemistry of these steps. The important observation[13] that only the 3*R*-(–)-mevalonolactone was a substrate for mevalonic acid kinase and that the 3*S*-enantiomer was inert, facilitated the determination of the absolute stereochemistry



33 34 35

(i) CD_3MgI; (ii) B_2H_6; (iii) H_2O_2, OH^-; (iv) CrO_3.

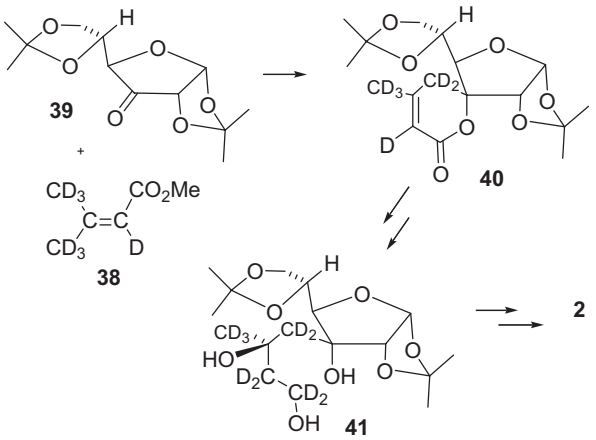
Scheme 12



36 37

(i) $LiAlD_4$; (ii) ^tBuOOH, $VO(acac)_2$; (iii) Ac_2O; (v) $RuCl_3$, $NaIO_4$.

Scheme 13



Scheme 14

of these steps. The stereospecific labels at C-2 and C-4 were introduced in several ways.

In the first approach the unsaturated acid **42** was separated[43] into its *cis* and *trans* isomers by the formation of a cyclic lactone **43** from the *cis* isomer. The separate alkenes were then converted into their benzhydrylamides, *e.g.* **44**. Reduction of their epoxides with lithium borodeuteride or borotritide proceeded in a *trans* manner such that the label which was introduced at C-4 **45** had a specific *anti* geometric relationship to the new tertiary alcohol at C-3. Since only the 3*R* enantiomer of mevalonic acid is a substrate for mevalonic acid kinase, this was in effect a synthesis of mevalonic acid with a chiral label at C-4 **46** and hence this would give information on the absolute stereochemistry of biosynthetic steps. The C-4 and C-2 positions of mevalonic acid can be interchanged by switching the carboxyl and carbinol arms of mevalonic acid. This inversion was achieved[44,45] by converting the carboxyl group into a methyl ester, oxidising the primary alcohol to an acid with zinc permanganate and then reducing the ester group with lithium borohydride to give **47**.

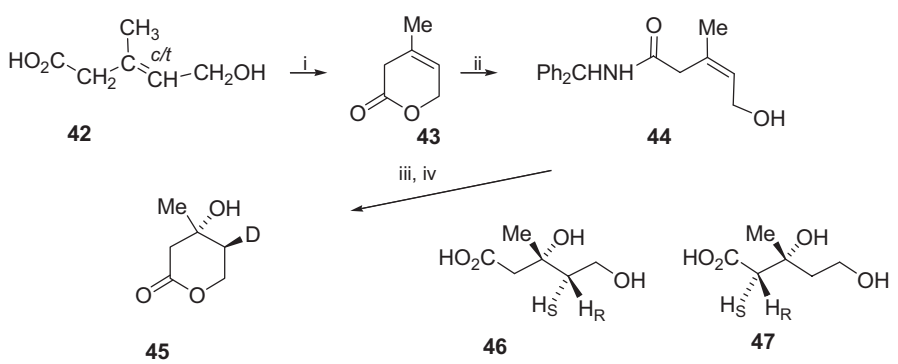
Another stereospecific synthesis[46] of [2- and 4-^{2}H] mevalonates was based on the reduction of chiral epoxides. Conjugate addition of dimethylcopper lithium to the acetylenic ester **48** followed by quenching the carbanion with deuterium oxide gave the labelled *Z*-unsaturated ester **49**. This was converted into an allylic alcohol by reduction with lithium aluminium hydride. Asymmetric epoxidation with the Sharpless reagent using (+)-diethyl tartrate gave the 2*S*,3*R*-epoxyalcohol **50** which was reduced with lithium aluminium hydride. The unprotected primary alcohol was then oxidised with alkaline potassium permanganate before acid-hydrolysis exposed the other hydroxyl group leading to the formation of (2*R*,3*R*)[2-^{2}H]mevalonolactone **51**. The diastereoisomeric [2*S*-^{2}H]mevalonate was obtained by quenching the dimethylcuprate adduct with water and reducing the epoxide with lithium aluminium deuteride.

The differing reactivities of ethoxyethyl and acetate protected derivatives were used to interchange C-l and C-5 and thus introduce the label at C-4. In this case the epoxide which was epimeric to **50** had to be prepared with (–)-diethyl tartrate. The epoxide was reduced with lithium aluminium hydride to give a diol and the primary alcohol was protected as its acetate. The acid-labile ethoxyethyl protecting group was removed and the resulting primary alcohol was oxidised to a carboxylic acid with chromium trioxide. Hydrolysis of the acetate afforded [3*R*,4*R*-4-^{2}H]meva1ono1actone.

Various other readily available allylic alcohols have been used as substrates for the Sharpless asymmetric epoxidation in order to prepare 3*R*-mevalonolactone. Reduction of the chiral epoxide **52** obtained[47] from the monoterpenoid, geraniol, with lithium aluminium deuteride gave the [2-^{2}H]-l,3-diol. Protection of the diol as a 1,3-dioxane and isomerisation of the 6,7-double bond via an epoxide gave **53**. Cleavage of the double bond and a selective protection:deprotection sequence exposed the C-l primary alcohol **54**. Oxidation and hydrogenolysis afforded (2*R*,3*R*)-[2-^{2}H]mevalonolactone.

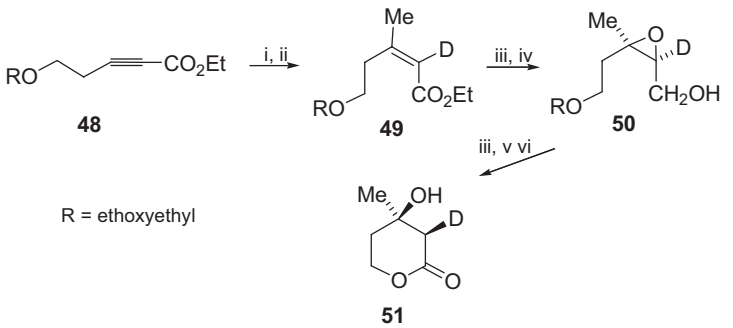
The stereospecific labelling of C-5 has been achieved enzymatically to give both the (5*R*)- and (5*S*)-mevalonates **55**. The C-5 aldehyde of mevaldic acid was produced by hydrolysis of both the acetal and the ester in **12**. Enzymatic reduction using pig or rat liver mevaldate reductase and [4(*R*)-4-^{3}H]NADPH as the source of the label afforded [5(*R*)-5-^{3}H]mevalonic acid.[48] Reduction of [5-^{3}H]mevaldic acid with this enzyme system and NADPH gave the [5(*S*)-5-^{3}H]isomer.[49] The [5-^{3}H]mevaldic acid was prepared using [4-^{3}H]-4,4-dimethoxybutan-2-one obtained by condensing methyl [^{3}H]formate with acetone and reaction with methanolic hydrogen chloride. It has been reported[50] that reduction of the co-enzyme A hemithioacetal of mevaldic acid with yeast hydroxymethylglutaryl co-enzyme A reductase and [4(*R*)-4-^{3}H]NADPH gave [5(*S*)-5-^{3}H]mevalonolactone.

Another chemo-enzymatic approach to [3(*RS*),5-(*S*)-5-^{3}H] mevalonolactone used[51,52] the more readily available liver alcohol dehydrogenase. In general, when an alcohol is formed by this enzyme from the corresponding aldehyde, the l-pro(*R*) hydrogen arises from the co-enzyme and l-pro(*S*) hydrogen is derived from the aldehyde. Since the starting material 3-methylbut-3-enal **56** readily isomerises to the conjugated αβ-unsaturated aldehyde, the labelled aldehyde was prepared under carefully controlled conditions. 3-Methylbut-3-enoyl chloride was converted into 4-methyl-2-oxopent-4-enyl



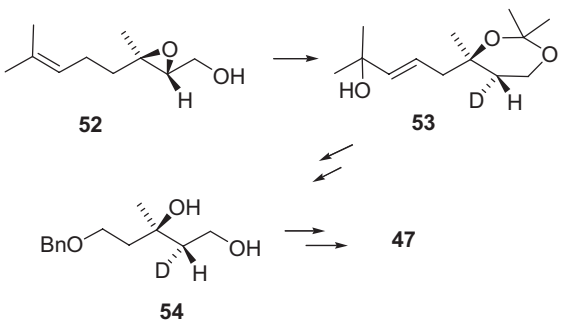
(i) H^+; (ii) Ph_2CHNH_2; (iii) $PhCO_3H$; (iv) $LiBD_4$;

Scheme 15

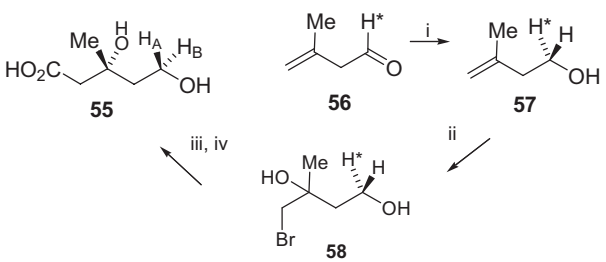


(i) Me_2CuLi; (ii) D_2O; (iii) $LiAlH_4$; (iv) ^tBuOOH, $Ti(O^iPr)_4$, (+)-DET; (v) alk. $KMnO_4$; (vi) H^+.

Scheme 16

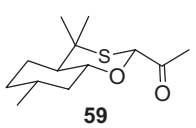


Scheme 17



(i) Liver alcohol dehydrogenase. NADH: (ii) HOBr; (iii) KCN; (iv) NaOH; H^+.

Scheme 18



Scheme 19

formate by treatment of the corresponding diazoketone with formic acid. This was easily reduced with either sodium borodeuteride or borotritide and hydrolysed to 4-methyl[2-^{2}H or 2-^{3}H]pent-4-en-l,2-diol. The diol represents a masked aldehyde. It was cleaved with aqueous sodium periodate to give a solution of labelled 3-methylbut-3-enal which could be reduced immediately with liver alcohol dehydrogenase and NADH. The resultant 1(*S*)[1-^{2}H or 1-^{3}H]-3-methylbut-3-en-l-ols **57** were converted into (3*RS*)-mevalonic acid via the bromohydrin **58**. The C-4 bromine was displaced with a cyanide which was then hydrolysed with sodium hydroxide.

In recent years. unlabelled samples of chiral mevalonolactone have been synthesised in order to validate other asymmetric synthetic strategies. Although these are outside the scope of this review, potentially some may be exploited to prepare labelled material. The methods include the asymmetric epoxidation and hydroxylation of different allylic alcohols[53-55] and the use of chiral auxiliaries such as methyl (S)-mandelate[56] and the 1,3-oxathiane **59** derived from (+)-pulegone.[57-59] Several chemo-enzymatic methods using the selective hydrolysis of various esters,[60-62] other desymmetrisation procedures[63] and chiral enzymatic epoxidations[64] have also been reported.

Over the past 50 years these labelled samples of mevalonolactone have played a key role in many studies of terpenoid biosynthesis. Although it is a relatively simple molecule, the ingenious design of routes to generate specifically labelled samples have made use of many modern synthetic transformations and reflect the changes in methodology that have taken place during this period.

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