Studies on a Synthesis of (*RS*)-Mevalonic Acid Lactone

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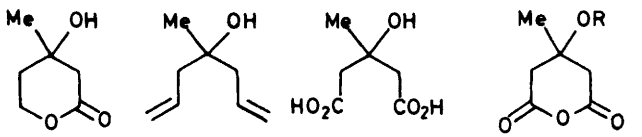
Full details of a high yielding synthesis of mevalonic acid lactone (**1**) which is of particular value in the preparation of 3- and/or 3'-labelled compounds are described. The key step, conversion of 3-hydroxy-3-methylpentane-1,5-dioic acid (**3**) into 3-hydroxy-3-methylpentane-1,5-dioic anhydride (**4**) using acetic anhydride, has been fully investigated, and an additional method using acetyl chloride and triethylamine is described.

Although a number of methods for the synthesis of isotopically labelled mevalonic acid lactone (**1**) have been described in recent years,[1–5] there are a few applicable to the synthesis of the 3'- and/or 3-labelled compounds. A short, high yielding synthesis of mevalonic acid lactone which enabled isotopic labels to be introduced into these positions was recently described.[6] In this synthesis ethyl acetate was treated with allylmagnesium bromide to give 4-hydroxy-4-methylhepta-1,6-diene (**2**) which was then converted by ozonolysis and further treatment of the crude product with hydrogen peroxide in acetic acid into 3-hydroxy-3-methylpentane-1,5-dioic acid (**3**). This in turn was converted into the corresponding anhydride (**4**) by being stirred with an 'excess' of acetic anhydride at room temperature, followed by sodium borohydride reduction of the anhydride to give mevalonic acid lactone (**1**). By starting with ethyl [2-^{13}C]acetate, [3'-^{13}C]mevalonic acid lactone could be obtained in 58% overall yield. As some problems with this synthetic procedure have been reported[7] we now describe full details of the procedure along with further studies to account for the reported problems, and a modification to facilitate the use of labelled starting materials.



(**1**) (**2**) (**3**) (**4**) R = H (**5**) R = Ac

Isotopically labelled acetate is more readily available and more conveniently handled as the sodium salt than the ethyl ester. The sodium salt can be converted into the ethyl ester in high yield by treatment with an excess of triethyl phosphate. However, separation of the ethyl acetate from the triethyl phosphate requires careful fractional distillation and it is more convenient to use tri-n-butyl phosphate and convert the sodium acetate into the corresponding n-butyl acetate.[8]

The Grignard reaction to convert ethyl (or n-butyl) acetate into (**2**) and its further conversion into the diacid (**3**) proceeds without difficulty and requires no further comment. However, problems appear to have been encountered in the next step, in which the diacid (**3**) is converted into the corresponding anhydride (**4**) by treatment with acetic anhydride. In a recent study,[7] the diacid (**3**) was found to be converted quantitatively into 3-acetoxy-3-methylpentane-1,5-dioic anhydride (**5**) with the desired product (**4**) being formed only as a transient intermediate. However, on systematic re-examination of the reaction, we find that the product formed depends on the relative concentrations of the diacid (**3**) and acetic anhydride, and on the reaction temperature. If fewer than 20 equivalents of acetic anhydride are used and the reaction temperature is below 30 °C the desired anhydride (**4**) is formed consistently in essentially quantitative yield. In a typical experiment, a solution of the diacid (**3**) (405 mg, 2.5 mmol) in acetic anhydride (3.5 ml, 35 mmol) was stirred at 18 °C. The course of the reaction was monitored by withdrawing small aliquots of the reaction mixture, removing the acetic anhydride immediately under reduced pressure, and determining the 80 MHz ^{1}H n.m.r. spectrum. As shown in Figure 1 the acid was converted smoothly into anhydride (**4**) with no trace of the acetate (**5**). After 24 h the initial suspension had turned into a clear solution. The excess of acetic anhydride was then removed to give a white solid shown by ^{1}H n.m.r. spectroscopy [Figure 2(a)] to be essentially pure anhydride (**4**). On repeating the reaction using the same batch of acid, but on double the scale, approximately 48 h were required for complete reaction. However, the time taken for complete reaction varied with the batch of acid used [normally the diacid (**3**) obtained from the ozonolysis step is used without further purification].

If 25 or more equivalents of acetic anhydride are used, the product is indeed the acetate (**5**) [Figure 2(b)]. Increasing the temperature to 30 °C (14 equivalents of acetic anhydride) still resulted in the anhydride (**4**) as the major product, but at 40 °C the acetate (**5**) was formed along with (**4**) as a 2:1 mixture. Interestingly, heating the diacid (**3**) to 100 °C with only 1.2 equivalents of acetic anhydride again gave anhydride (**4**) as the sole product.

Although we find the use of acetic anhydride the most convenient method for the production of anhydride (**4**), an alternative method not subject to the same variability is to react the diacid with acetyl chloride and triethylamine in tetrahydrofuran (THF) at 0 °C. Reaction is again quantitative and is complete in only 2 h. The acetate (**5**) can be more conveniently prepared from the diacid (**3**) by heating in acetyl chloride at 50 °C for 4 h. Removal of excess of acetyl chloride gives a quantitative yield of (**5**). Anhydride (**4**) can also be converted readily into the corresponding acetate (**5**) by being stirred at room temperature with a slight excess of acetyl chloride.

Treatment of the anhydride (**4**) with sodium borohydride in propan-2-ol, acidification, and continuous extraction with ether gave almost pure mevalonic acid lactone which was purified finally by column chromatography on silica using hexane–ether as eluant.

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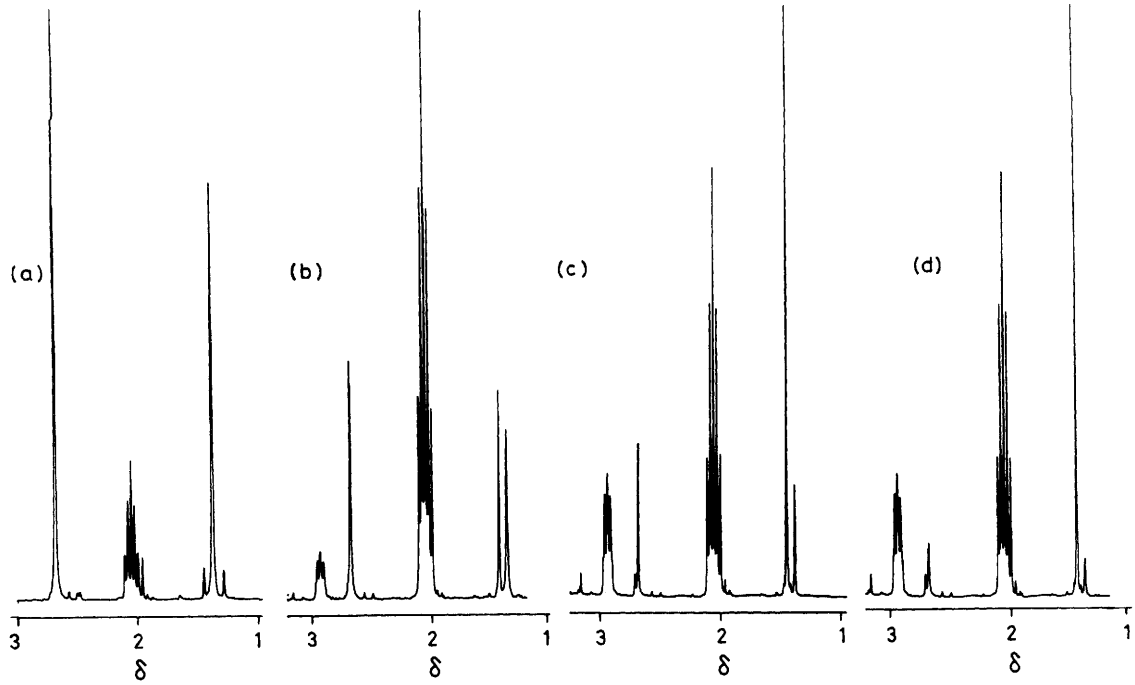

Figure 1. 80 MHz ^{1}H n.m.r. spectra of the reaction mixture from 3-hydroxy-3-methylpentane-1,5-dioic acid (**3**) with acetic anhydride (14 equiv.) at room temperature. Samples were taken at (a) $t = 0$, (b) $t = 2$, (c) $t = 4$, and (d) $t = 6$ h. The excess of acetic anhydride was removed under reduced pressure and the resulting white solid was dissolved in [$^2H_6$]acetone and the spectra determined on a Bruker WP80 spectrometer.

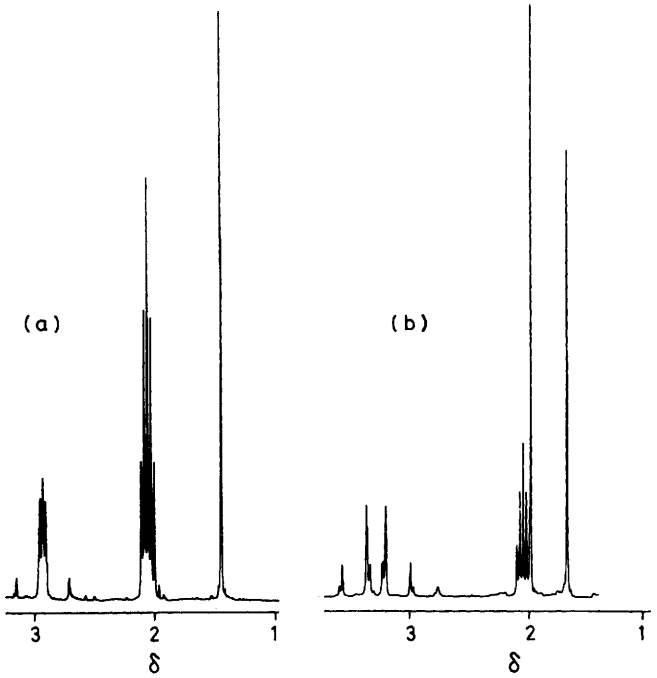

Figure 2. 80 MHz ^{1}H n.m.r. spectra in [$^2H_6$]acetone of (a) 3-hydroxy-3-methylpentane-1,5-dioic anhydride (**4**), and (b) 3-acetoxy-3-methylpentane-1,5-dioic anhydride (**5**).

Experimental

M.p.s. were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H N.m.r. spectra were determined on either Varian EM360, Bruker WP80, or Bruker WP200 spectrometers for deuteriochloroform or hexadeuterioacetone solution. I.r. spectra were determined on a Perkin-Elmer 257 spectrophotometer as KBr discs.

Conversion of Sodium Acetate into n-Butyl Acetate.—Sodium acetate (5 g, 60 mmol) was mixed with tri-n-butyl phosphate (20 ml) and the mixture was heated under reflux for 5 h on an oil-bath at 200—220 °C. The viscous mixture was cooled to room temperature, the upper end of the reflux condenser was sealed through a liquid-nitrogen-cooled trap to a vacuum pump, and the product ester was distilled into the cold trap by heating the reaction flask to 100—160 °C for 2.5 h at 1 mmHg pressure with cold water running in the reflux condenser. n-Butyl acetate (6.8 g, 96%) was obtained.

4-*Hydroxy*-4-*methylhepta*-1,6-*diene* (**2**).—A mixture of ethyl acetate (0.5 g) and allyl bromide (2.06 g) in diethyl ether–THF (1:1; 10 ml) was added dropwise to a stirred mixture of magnesium turnings (0.55 g) in diethyl ether–THF (1:1; 2 ml). After the mixture had been stirred overnight, crushed ice (7 g) was added and the mixture was acidified with 6M-sulphuric acid. The resulting solution was extracted with diethyl ether, and the extract was washed with saturated potassium hydrogen carbonate solution and dried over Na_2SO_4. Removal of the solvent gave a yellow oil which was distilled at water-pump pressure to yield the dienol (**2**) as an oil (0.73 g), b.p. 90—92 °C; $\delta_H(CDCl_3)$ 1.18 (3 H, s), 1.8 (1 H, br s, exchangeable), 2.23 (4 H, d, J 7 Hz), and 5.00—6.00 (6 H, m).

3-*Hydroxy*-3-*methylpentane*-1,5-*dioic Acid* (**3**).—Ozone was passed through a stirred solution of the alcohol (**2**) (0.51 g) in a mixture of methylene dichloride and acetic acid (10:1; 11 ml) at −78 °C until a blue colour appeared. The reaction mixture was then allowed to warm up to room temperature and acetic acid (10 ml) was added. After concentration of the reaction mixture to about 5 ml, more acetic acid (10 ml) and a 30% solution of hydrogen peroxide (4 ml) were added and the mixture was heated under a reflux for 13 h. Evaporation of the solvent gave the diacid (**3**) as an oil (0.55 g) which slowly solidified. Recrystallisation from diethyl ether gave the acid as needles, m.p. 110—111 °C (lit.,[3] 110—111 °C); $\delta_H[(CD_3)_2CO]$ 1.38 (3 H, s),

2.68 (4 H, s), and 6.15 (*ca.* 2 H, br s). Treatment with diazomethane gave the dimethyl ester which showed $\delta_H(CDCl_3)$ 1.39 (3 H, s), 2.73 (4 H, s), and 3.75 (6 H, s).

Reactions of 3-*Hydroxy*-3-*methylpentane*-1,5-*dioic acid* (**3**) *with Acetic Anhydride*.—These were carried out using a wide variety of relative concentrations of diacid (**3**) to acetic anhydride (1:1 to 1:25). Some representative experiments are detailed below.

(a) 14 *Equivalents of acetic anhydride at* 18 °C. A mixture of diacid (**3**) (810 mg, 5 mmol) and acetic anhydride (6.6 ml, 70 mmol) was stirred at room temperature. After 72 h the initial suspension had turned into a clear solution. The excess of acetic anhydride was removed under high vacuum to give a white solid (817 mg) which was recrystallised from diethyl ether–light petroleum (b.p. 30—40 °C) to give 3-hydroxy-3-methylpentane-1,5-dioic anhydride (**4**) as needles (673 mg), m.p. 102—103 °C (lit.,[9] 101—102.5 °C); $\nu_{max.}$ 3 320, 1 810, 1 768, and 1 755 cm^{-1}; δ_H (200 MHz) 1.44 (3 H, s), 2.80, 2.90, 2.98 and 3.06 (4 H, AA'BB'), and 4.67 (1 H, br s, exchangeable) (Found: C, 50.1; H, 5.45. Calc. for $C_6H_8O_4$: C, 50.00; H, 5.56%). Similar results were obtained using between 5 and 20 equivalents of acetic anhydride.

(b) 1.5 *Equivalents of acetic anhydride at* 100 °C. A solution of the diacid (**3**) (405 mg) in acetic anhydride (0.35 ml) was stirred and heated at 100 °C for 1.5 h. After 45 min a clear solution was obtained. Removal of excess of acetic anhydride gave a pale solid which was recrystallised as above to give the anhydride (**4**) as needles (300 mg).

(c) 25 *Equivalents of acetic anhydride at* 18 °C. Reaction between the diacid (**3**) (162 mg, 1 mmol) and acetic anhydride (2.36 ml, 25 mmol) at room temperature gave a clear solution after the mixture had been stirred for 12 h. Removal of excess of acetic anhydride gave a solid (216 mg) which was recrystallised from diethyl ether to give 3-acetoxy-3-methylpentane-1,5-dioic acid anhydride (**5**) as prisms (180 mg), m.p. 83—85 °C (lit.,[10] 85 °C); $\nu_{max.}$ 1 810, 1 775, 1 760, and 1 735 cm^{-1}; δ_H (80 MHz) 1.68 (3 H, s), 1.98 (3, H, s), and 2.99, 3.20, 3.36 and 3.56 (4 H, AA'BB').

(d) 14 *Equivalents of acetic anhydride at* 40 °C. The diacid (**3**) (405 mg, 2.5 mmol) in acetic anhydride (3.3 ml, 35 mmol) was stirred and heated at 40 °C. The usual work-up gave a pale solid (392 mg) which was shown by n.m.r. spectroscopy to consist of a 2:1 mixture of the acetate (**5**) and the anhydride (**4**).

Reaction of 3-*Hydroxy*-3-*methylpentane*-1,5-*dioic Acid* (**3**) *with Acetyl Chloride and Triethylamine*.—Triethylamine (0.35 ml) was added to a solution of the diacid (**3**) (405 mg) in dry THF (30 ml) and the mixture was cooled to 0 °C in an ice-bath. A solution of acetyl chloride (0.2 ml) in dry (20 ml) was then added dropwise to the stirred mixture during *ca.* 5 min. The resulting suspension was stirred for 2 h at 0 °C. The solid residue was filtered off and washed with (2 ml). The filtrate and washings were then concentrated at 30 °C on a rotary evaporator to give a pale pink solid (415 mg) which was recrystallised from diethyl ether–light petroleum (b.p 30–40 °C) to give the anhydride (**4**) as needles (350 mg), m.p. 102—103 °C.

Reaction of 3-*Hydroxy*-3-*methylpentane*-1,5-*dioic Acid* (**3**) *with Acetyl Chloride*.—Diacid (**3**) (0.6 g) was refluxed in acetyl chloride (5 ml) for 4 h. The excess of acetyl chloride was removed under reduced pressure to give a pale solid which was recrystallised from diethyl ether to give the acetate (**5**) as crystals (0.55 g), m.p. 75—76 °C.

Mevalonic Acid Lactone (**1**).—The crude anhydride (**4**) (0.7 g) was dissolved in propan-2-ol (20 ml) and the solution was added dropwise to sodium borohydride (0.4 g) cooled in an ice-bath. The reaction mixture was stirred overnight at room temperature. After removal of the solvent, water (10 ml) was added and the mixture was acidified to pH 2 in an ice-bath. The solution was extracted continuously with diethyl ether for 45 h. The extract was dried (Na_2SO_4) and the solvent removed on a rotary evaporator to give an oil which was shown by t.l.c. to have one component, corresponding to mevalonic acid lactone. Column chromatography on Malinckrodt silica AR-CC-7 (20 g) and elution with hexane–diethyl ether (2:8) gave pure mevalonic acid lactone (**1**) (300 mg).

Acknowledgements

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