Reinvestigation of a Synthesis of (*R,S*)-Mevalonolactone

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An n.m.r. study of the reaction of 3-hydroxy-3-methylpentane-1,5-dioic acid (5) with excess of [$^2H_6$]-acetic anhydride is described. It has shown that 3-hydroxy-3-methylpentane-1,5-dioic acid anhydride (2), previously described by Scott and Shishido [1] as an intermediate in their synthesis of [3′-^{13}C]mevalonolactone, is formed only transiently, along with 3-acetoxy-3-methylpentane-1,5-dioic acid (6). Both intermediates eventually give 3-acetoxy-3-methylpentane-1,5-dioic acid anhydride (3).

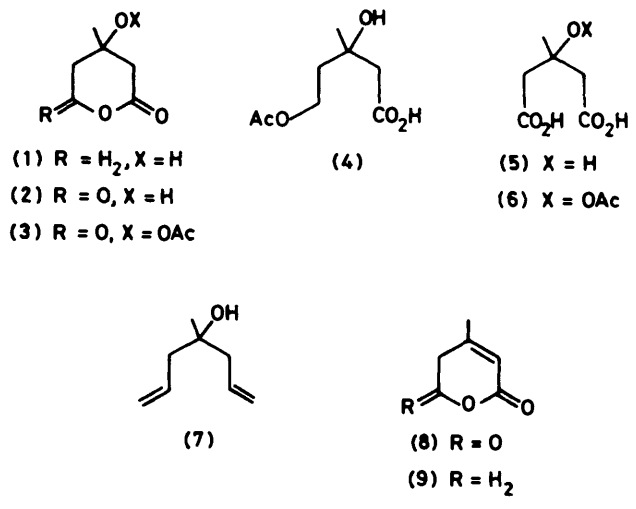
To obtain (*R,S*)-mevalonolactone, sodium borohydride reduction of 3-hydroxy-3-methylpentane-1,5-dioic acid anhydride (2), prepared from the diacid (5) and *N,N*′-dicyclohexylcarbodi-imide, is shown to be better than reduction of 3-acetoxy-3-methylpentane-1,5-dioic acid anhydride (3).

The biologically important mevalonolactone (1) has been synthesised in many ways since it was first identified in extracts of distillers' solubles.[2,3] Syntheses have largely concentrated on methods of introducing isotopic labels into the molecule, for use in biosynthetic studies. Amongst several recent syntheses [1,4-8] is that of Scott and Shishido [1] for the preparation of [3′-^{13}C]-labelled mevalonolactone. This synthesis was of interest to us in connection with the investigation of the biosynthesis of the gibberellins, a group of diterpene acids.

The published route [1] utilised the alcohol diene (7) formed by reaction of allylmagnesium bromide with ethyl acetate. The alcohol (7) was then ozonised, and oxidised further using acetic acid–hydrogen peroxide to the diacid (5) which was cyclised in an excess of acetic anhydride at room temperature during 14 h to give the anhydride alcohol (2). Reduction, using sodium borohydride in propan-2-ol, yielded (*R,S*)-mevalonolactone (1). Thus, by using [2-^{13}C]ethyl acetate, [3′-^{13}C]-mevalonolactone was prepared.[1]

In our hands, however, the cyclisation of the diacid (5) always proceeded to give the anhydride acetate (3) in an isolated yield of 97%. This compound was recognised by its characteristic ^{1}H n.m.r. spectrum which, in deuteriochloroform, showed a singlet at δ 1.70, assigned to the *C*-methyl group, a singlet at δ 2.03, assigned to the acetate methyl group, and an AA′BB′ system at *ca.* δ 2.76 and *ca.* 3.54, assigned to the non-equivalent methylene protons, *cis* and *trans* to the methyl group. Thus the presence of the acetoxy group in the anhydride (3) profoundly affected the ^{1}H n.m.r. spectrum as compared with that of the 3-hydroxy anhydride (2) (see later) which, in hexadeuterioacetone, showed a singlet at δ 1.40, assigned to the *C*-methyl group, and a singlet at δ 2.94, assigned to the four methylene protons. Other data for the anhydride (3) (i.r., m.p.) were in agreement with those of Adams and Van Duuren,[9] and the mass spectrum showed the expected losses from the absent molecular ion. In addition, on being heated at 100 °C for 24 h, the anhydride acetate (3) was converted into the unsaturated anhydride (8) [9] which showed the expected ^{1}H n.m.r. spectrum. This latter compound was also formed when the diacid (5) was refluxed in excess of acetic anhydride for 1.5 h.

These results prompted further examination of the cyclisation reaction. Since the product (3) was easily recognisable by its ^{1}H n.m.r. spectrum, the reaction between the diacid (5) and hexadeuterioacetic anhydride was performed in an n.m.r. tube and was followed by taking spectra at intervals. Hexadeuterioacetic anhydride, used as the cyclising reagent, was made by the reaction of trideuterioacetyl chloride with sodium trideuterioacetate, each of these having been made from tetradeuterioacetic acid. Spectra were recorded over a period of two days, although very little change occurred after 24 h. The results are indicated in the Figure, where only the portion of the spectrum between δ 1.0 and 4.0 is shown in each case. The peaks at δ *ca.* 2 are due to residual protons in [$^2H_6$]acetic anhydride, [$^2H_3$]acetic acid, and [$^2H_3$]-acetoxy groups.



The peaks marked A are due to starting material (5) in all spectra; those marked B are assigned to the acetate anhydride (3) by comparison with authentic material, although the chemical shifts are slightly different owing to changes in solvent polarity.

It can be seen from Figure 1 that the reaction proceeds from the diacid (5) to the anhydride acetate (3) with the formation of two intermediates (with corresponding peaks in the spectra labelled C and D). Intermediate C appears early in the reaction, but has virtually disappeared when t = 2.3 h. In contrast, intermediate D increases in concentration until t = 5 h, then decreases to zero concentration when t = 22 h. From the chemical shift positions of the *C*-methyl peaks in the region δ 1.0—2.0, it appears that compound D is acetylated since its *C*-methyl peak is deshielded, whereas compound C is not. Thus C and D were assigned the structures (2) and (6), respectively. The n.m.r. spectrum of authentic (2) (see Experimental section) supports this assignment, although the chemical shifts are slightly different, again owing to solvent polarity differences.

Thus, it appears that the desired product (2) was never formed exclusively, and occurred for only a short period. Also, since formation of (2) was well advanced when that of (6) was

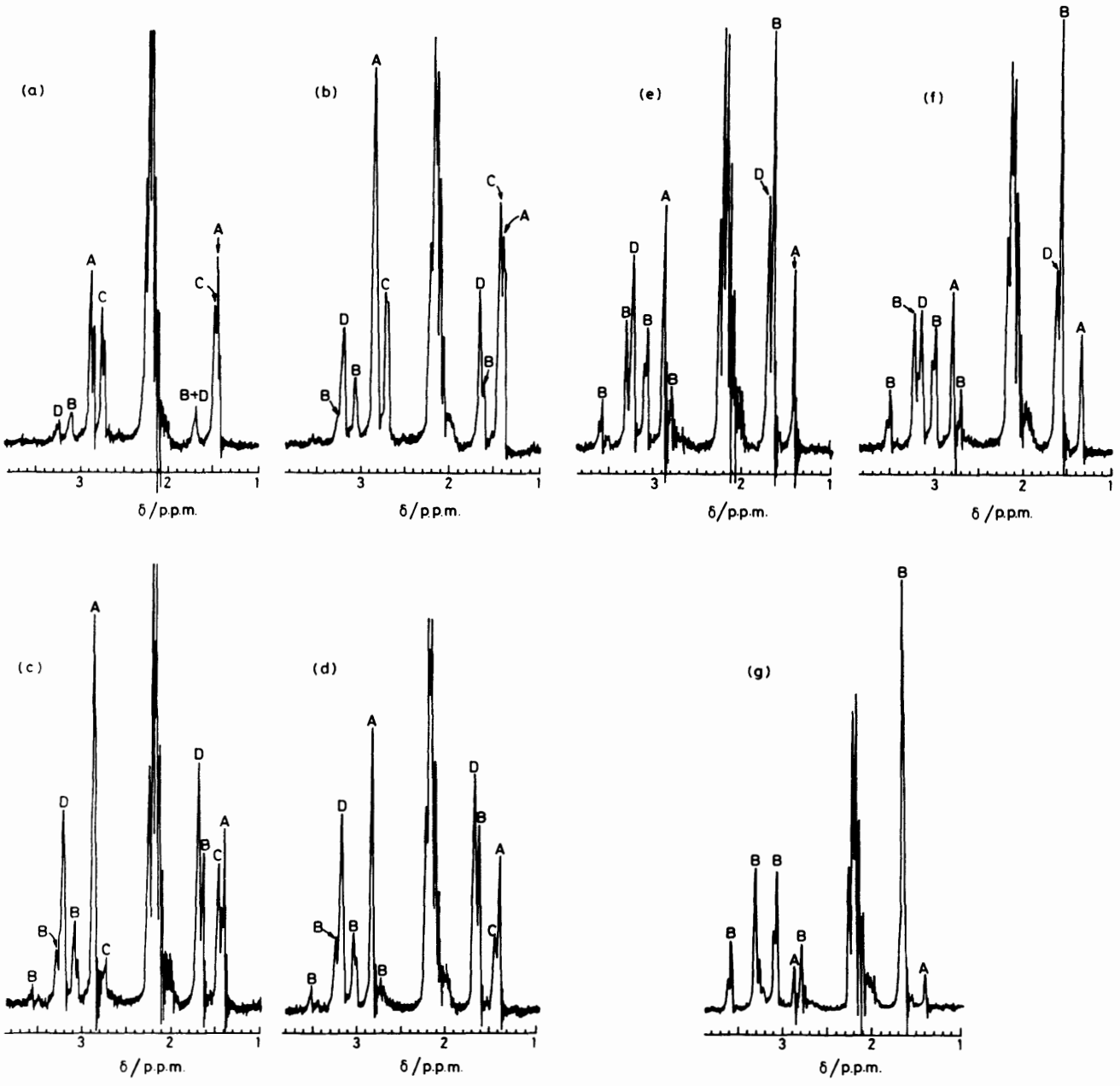


Figure. ^{1}H N.m.r. spectra of the reaction of 3-hydroxy-3-methylpentane-1,5-dioic acid and [$^2H_6$]acetic anhydride: (a) t = 0.25 h; (b) t = 0.6 h; (c) t = 1.6 h; (d) t = 2.3 h; (e) t = 5 h; (f) t = 7 h; (g) t = 22 h. Peaks A correspond to compound (5), B to compound (3), C to compound (2) and D to compound (6)

not yet obvious (*i.e.* at t = 0.25 h), it is logical to conclude that the reactions to produce (2) and (6) are parallel and not sequential, since (2) should not give rise to (6) except by reversion to diacid (5), under these reaction conditions.

The 3-hydroxy anhydride (2) was, however, prepared in good yield by reaction of the diacid (5) with *N,N'*-dicyclohexylcarbodi-imide; thus the production of mevalonolactone (1) by reduction of either (2) or (3) was compared. In each case the reduction was performed using 2.5 mol equiv. of sodium borohydride per mol of anhydride (2) or (3). It was found that such reduction of the crude alcohol anhydride (2) gave mevalonolactone (1) as the sole product which, after distillation, gave pure (1) in a yield of 72% for the last two steps. In contrast, reduction of the acetate anhydride (3) gave a mixture of three products, which were separated by column chromatography. The major product was found to be mevalonolactone (1), but an appreciable amount of mevalonic acid 5-acetate (4) and a small amount of the elimination product (9) were formed in addition. Thus, our preferred method for the synthesis of [3'-^{13}C]-labelled mevalonolactone involved the preparation of the hydroxy anhydride (2) (labelled at the methyl group with ^{13}C) from the diacid (5) by reaction with *N,N'*-dicyclohexylcarbodi-imide and subsequent sodium borohydride reduction. Using this method, [3'-^{13}C]mevalonolactone containing 0.89 atoms ^{13}C per molecule was obtained in 57% overall yield from [2-^{13}C]-ethyl acetate.

It should be noted that the reduction of the anhydrides (2) and (3) is critically dependent on the order of addition of reagents. High yields of mevalonolactone (1) were only

obtained when the sodium borohydride was stirred with propan-2-ol for 30 min before addition of the appropriate anhydride dissolved in propan-2-ol. The addition of solid sodium borohydride to the anhydride dissolved in propan-2-ol led to the formation of a complex mixture of products (by ^1H and ^{13}C n.m.r., t.l.c., and g.l.c.), the major component of which was not mevalonolactone.

Experimental

General Procedures.—M.ps were determined on a Kofler hot stage and are uncorrected. ^1H and ^{13}C N.m.r. spectra were run on either Varian T-60, Jeol PS-100, or Jeol FX-90Q spectrometers and refer to $CDCl_3$ solutions with internal Me_4Si unless otherwise stated. I.r. spectra were run on a Perkin-Elmer 197 spectrophotometer either as Nujol mulls or in solution. Mass spectra were determined at 70 eV with a source temperature of 200 °C unless otherwise stated. Analytical t.l.c. plates were visualised either under u.v. light or by exposure to iodine vapour.

Reaction of Ethyl Acetate with Allylmagnesium Bromide.—A mixture of ethyl acetate (0.5 g) and allyl bromide (1.82 g) in diethyl ether–tetrahydrofuran (1 : 1; 20 ml) was added during 40 min with vigorous stirring to dry magnesium turnings (0.36 g) in diethyl ether–tetrahydrofuran (1 : 1; 10 ml). After being heated under reflux for 6 h, water (5 ml) was added, followed by 6M-hydrochloric acid (5 ml) with ice-cooling. The solution was extracted with diethyl ether (3 × 50 ml) and the extract was washed with saturated sodium hydrogen carbonate solution (50 ml) and dried ($MgSO_4$). Concentration under reduced pressure yielded the alcohol diene (7) as an oil (0.70 g): δ_H 1.18 (s, 3H, Me), 1.82 (br s, 1 H, OH), 2.23 (d, J 7.5 Hz, 4 H, $2CH_2$), and 5.00—6.03 (6 H, complex vinylic); δ_C 26.65, 46.21, 71.67, 118.59, and 133.92 p.p.m.; $\nu_{max.}$ (film) 3 450br, 3 090, and 1 645 cm^{-1}; m/z 85 (34) and 43 (100); b.p. 28—30 °C at 1.4 mmHg.

Oxidation of 4-Hydroxy-4-methylhepta-1,6-diene (7).—The alcohol diene (7) (0.70 g) was dissolved in dichloromethane–acetic acid (10 : 1; 100 ml) and cooled to −78 °C. Ozone was then passed through the solution until a permanent blue colour persisted. The solution was then allowed to warm to room temperature and the solvent was removed under reduced pressure to yield a colourless oil. This oil was dissolved in acetic acid–hydrogen peroxide (30%) (60 ml of 3 : 4, v/v) and heated under reflux for 6 h. On removal of the solvent the diacid (5) remained as an oil (0.72 g) which slowly solidified: δ_H (C_5D_5N) 1.84 (s, 3H, Me), 3.27 (s, 4H, $2CH_2$), and 11.55 (br s, *ca.* 2H, $2CO_2H$); δ_C(C_5D_5N) 28.28, 46.48, 70.05, and 174.7 p.p.m.; $\nu_{max.}$ (Nujol mull) 3 250, 3 200—2 300, and 1 710br cm^{-1}; m/z 147 (9), 129 (52), 111 (29), 103 (76), 87 (36), 85 (94), and 43 (100). A small portion of the diacid (5) was converted into its dimethyl ester by dissolution in methanol and treatment with ethereal diazomethane: δ_H 1.36 (s, *ca.* 2 H, Me), 2.68 (s, 4H, $2CH_2$), and 3.70 (s, 6H, 2MeO); m/z 175 (7), 159 (2), 143 (33), 141 (19), 117 (100), 101 (19), 85 (52), and 43 (80).

Reaction of 3-Hydroxy-3-methylpentane-1,5-dioic Acid (5) *with Acetic Anhydride.*—Acetic anhydride (20 ml) was added to the diacid (5) (0.78 g) and the mixture was stirred at room temperature for 24 h. Removal of the solvent under reduced pressure yielded 3-acetoxy-3-methylpentane-1,5-dioic acid anhydride (3) as a pale brown oil (0.87 g) which crystallised on standing in a vacuum desiccator. Recrystallisation from diethyl ether gave clear prisms, m.p. 83—84 °C (lit.,[9] 85 °C); δ_H 1.70 (s, 3 H, Me), 2.03 (s, 3 H, $OCOCH_3$), *ca.* 2.76 (m, 2 H, 2CH), and *ca.* 3.54 (m, 2 H, 2CH); δ_C (hexadeuterioacetone) 21.70, 23.98, 41.40, 77.2, 165.83 and 170.78 p.p.m.; $\nu_{max.}$ ($CHCl_3$)[9] 1 826, 1 780 and 1 750 cm^{-1}; m/z 126 (39), 100 (18), 82 (20), 60 (23), and 43 (100); at 60 °C source temperature m/z = 126 decreased markedly in intensity.

Action of Heat on 3-Acetoxy-3-methylpentane-1,5-dioic Acid Anhydride (3).—The acetate anhydride (3) (20 mg) was heated at 100 °C for 24 h. The resultant oil (15 mg) was crystallised from diethyl ether to give (8) as needles, m.p. 83—84 °C (lit.,[9] 85 °C); δ_H 2.08 (3 H, Me), 3.46 (2 H, CH_2), and 6.06 (1 H, vinylic) (each complex m); $\nu_{max.}$ ($CHCl_3$)[9] 1 804, 1 755, and 1 665 cm^{-1}; m/z 126 (2), 82 (100), 54 (35), and 39 (66).

Alternative Preparation of 3-Methylpent-2-ene-1,5-dioic Acid Anhydride (8).—Acetic anhydride (15 ml) was added to the diacid (5) (0.355 g) and the solution was heated under reflux for 1.5 h. Removal of solvent under reduced pressure yielded a brown oil (0.4 g) which was crystallised from diethyl ether. The crystals had properties identical with those of the compound formed by the action of heat on the 3-acetoxy anhydride (3).

Preparation of 3-Hydroxy-3-methylpentane-1,5-dioic Acid Anhydride (2).—The diacid (5) (0.72 g) was dissolved in the minimum volume of acetone and treated with *N,N'*-dicyclohexylcarbodi-imide (1.035 g, 1 mol equiv.) dissolved in the minimum volume of acetone. The solution was stirred at 46 °C for 3 h, cooled to 0 °C and the precipitated *N,N'*-dicyclohexylurea was filtered off. Removal of the solvent under reduced pressure yielded an oil (0.695 g). This contained a small amount of the *N,N'*-dicyclohexylurea (by i.r.) but gave a satisfactory ^1H n.m.r. spectrum: δ([$^2H_6$]acetone) 1.40 (s, 3H, Me), 3.09 (s, 4H, $2CH_2$), and 4.55 (s, *ca.* 2H, OH).

Preparation of Sodium Trideuterioacetate.—[$^2H_4$]Acetic acid (3.47 g) was treated with 10M-sodium hydroxide solution (5.4 ml, 1 mol equiv.) with ice-cooling. After 0.5 h the solution was boiled to dryness, and the resulting white solid was then fused to give sodium [$^2H_3$]acetate (4.7 g).

Preparation of Trideuterioacetyl Chloride.—Phosphorus trichloride (2.55 ml) was slowly added with cooling to [$^2H_4$]-acetic acid (5.41 g). After 45 min the solution was heated to 45 °C and kept at this temperature for 30 min. Crude [$^2H_3$]-acetyl chloride was then distilled at 47—50 °C. The distillate was treated with acetic acid (3 drops) and redistilled to give pure [$^2H_3$]acetyl chloride (3.4 g), b.p. 48—50 °C.

Preparation of Hexadeuterioacetic Anhydride.—[$^2H_3$]-Acetyl chloride (3.31 g) was added during 10 min, with ice-cooling, to sodium [$^2H_3$]acetate. The mixture was then distilled using a free flame, collecting the fraction with b.p. 135—140 °C. This distillate was then redistilled to give [$^2H_6$]acetic anhydride (3.95 g), b.p. 138—140 °C: $\nu_{max.}$ (liquid film) 2 270, 2 130, 1 825, 1 755, 1 165, 1 050, and 1 015 cm^{-1}.

Reaction of 3-Hydroxy-3-methylpentane-1,5-dioic Acid (5) *with Hexadeuterioacetic Anhydride.*—The diacid (5) (25 mg) was placed in a 5-mm O.D. n.m.r. tube and [$^2H_6$]acetic anhydride (0.4 ml) was added. A small amount of tetramethylsilane was added as reference, and the tube was tightly capped. Spectra were then run at intervals. It was observed that the diacid had all dissolved when t = 0.6 h.

Reduction of 3-Hydroxy-3-methylpentane-1,5-dioic Acid Anhydride (2) *with Sodium Borohydride in Propan-2-ol.*—The crude product (2) (0.695 g) was dissolved in propan-2-ol (10 ml) and added dropwise to a suspension of sodium borohydride (0.42 g, 2.5 mol equiv.) in propan-2-ol (10 ml) which had been stirred for 0.5 h. The mixture was then stirred for 24 h at room temperature and the solvent was removed under reduced pressure. The resulting solid was dissolved in water (10 ml) and acidified to pH 2, under ice-cooling, using 2M-hydrochloric acid. This solution was stirred for 24 h, then continuously extracted with diethyl ether for 72 h. The diethyl ether extract was dried ($MgSO_4$) and concentrated under reduced pressure. The product was distilled at 100 °C at 0.01 mmHg and the resultant clear oil (0.42 g) was pure by t.l.c., g.l.c., (OV 210 at 100 °C), and h.p.l.c., and its ^1H and ^{13}C n.m.r. and mass spectra were identical with those of authentic mevalonolactone (1).

Reduction of 3-Acetoxy-3-methylpentane-1,5-dioic Acid Anhydride (3) *with Sodium Borohydride in Propan-2-ol.*—The acetate anhydride (3) (0.8 g) was added to sodium borohydride (0.41 g, 2.5 mol equiv.) stirred in propan-2-ol (10 ml) and worked-up and extracted as for the preceding experiment to yield a yellow oil which was chromatographed on silica gel (15 g), eluted with light petroleum (b.p. 60—80 °C) with an increasing proportion of ethyl acetate. On concentration, the fraction with 50% ethyl acetate gave an oil (80 mg) which was found by t.l.c. to contain two closely running compounds. The least polar compound was fluorescent under u.v. light, although the more polar compound was most abundant (as judged by the extent of staining by iodine vapour). The ^1H n.m.r. spectrum of the mixture showed major peaks at 1.35 (s), 1.95 (t, *J* 7 Hz), 2.05 (s), 2.50 (s), and 4.25 (t, *J* 7 Hz) plus minor peaks indicating the presence of an olefinic compound. The ^{13}C n.m.r. spectrum showed major peaks at 176.1 (s in off-resonance spectrum), 171.4 (s), 70.3 (s), 60.9 (t), 44.9 (t), 39.8 (t), 27.0 (q), and 21.1 (q), plus minor peaks in the region 120—125 p.p.m. These data strongly suggest that this fraction contained a mixture of mevalonic acid 5-acetate (4) plus the α,β-unsaturated product (9). The fractions with 75, 85, and 100% ethyl acetate were found to contain pure mevalonolactone (1) (total of 230 mg), identical with an authentic sample by ^1H n.m.r. and t.l.c.

[3′-^{13}C]*Mevalonolactone.*—Using the reaction sequence, ethyl acetate ⟶ (7) ⟶ (5) ⟶ (2) ⟶ (1), [3′-^{13}C]mevalonolactone containing 0.89 atoms ^{13}C per molecule was prepared in 57% overall yield from [2-^{13}C]ethyl acetate. (All intermediate compounds on the route to mevalonolactone were sufficiently pure to be used directly without purification).

Acknowledgements

We wish to thank the S.E.R.C. for a research studentship to P. L.

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Received 1*st November* 1982; *Paper* 2/1844