Diacetone-glucose architecture as a chirality template. Part 9.[1] Enantioselective synthesis of (*R*)-mevalonolactone and (*R*)-[$^2H_9$]mevalonolactone on carbohydrate template

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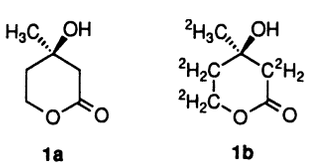
A highly enantioselective synthetic methodology for (*R*)-mevalonolactone has been developed based upon the chirality-transcription approach using a chiral template, diacetone-D-glucos-3-ulose 2. (*R*)-Mevalonolactone 1a is prepared from ketone 2 in 5 steps in 11% overall yield. This methodology is further applied to the synthesis of fully deuteriated (*R*)-[$^2H_9$]mevalonolactone 1b starting from ketone 2 and methyl [$^2H_7$]senecioate 7.

Introduction

(*R*)-Mevalonate is ubiquitous in that it is the very first biosynthetic precursor to various vertebrate and invertebrate hormones, through-membrane transporters, membrane-anchors of proteins including oncogene products, membrane core lipids of certain bacteria, visual pigments, vitamins and an enormous number of terpenoids in microorganisms, plants and animals.[2,3] The major biosynthetic pathways to these metabolites have been studied for decades. Since tracer methodology is a vital approach in this field, various isotopomers of mevalonate and mevalonolactone have been prepared to date.[4] Most of the isotopically labelled mevalonate and mevalonolactone were synthesized in racemic forms, rather than in optically active forms. Further, no method has been reported up to now for the synthesis of fully deuteriated (*R*)-[$^2H_9$]mevalonate or (*R*)-[$^2H_9$]-mevalonolactone, which is apparently useful or amenable to address certain issues of mevalonate metabolism. We here pursued an enantioselective synthesis of (*R*)-mevalonolactone **1a** and (*R*)-[$^2H_9$]mevalonolactone **1b**.



1a **1b**

Structure of mevalonolactone **1a** and [$^2H_9$]mevalonolactone **1b**

Exploitation of efficient and useful methodology for chiral synthesis has been a major issue in synthetic organic chemistry, and chiral synthesis of mevalonate derivatives is no exception.[5,6] We have been involved in developing a chirality-transcription approach on a carbohydrate template for various biochemically important metabolites.[7–9] This paper describes an efficient and highly enantioselective synthesis of (*R*)-mevalonolactone **1a** using this methodology.

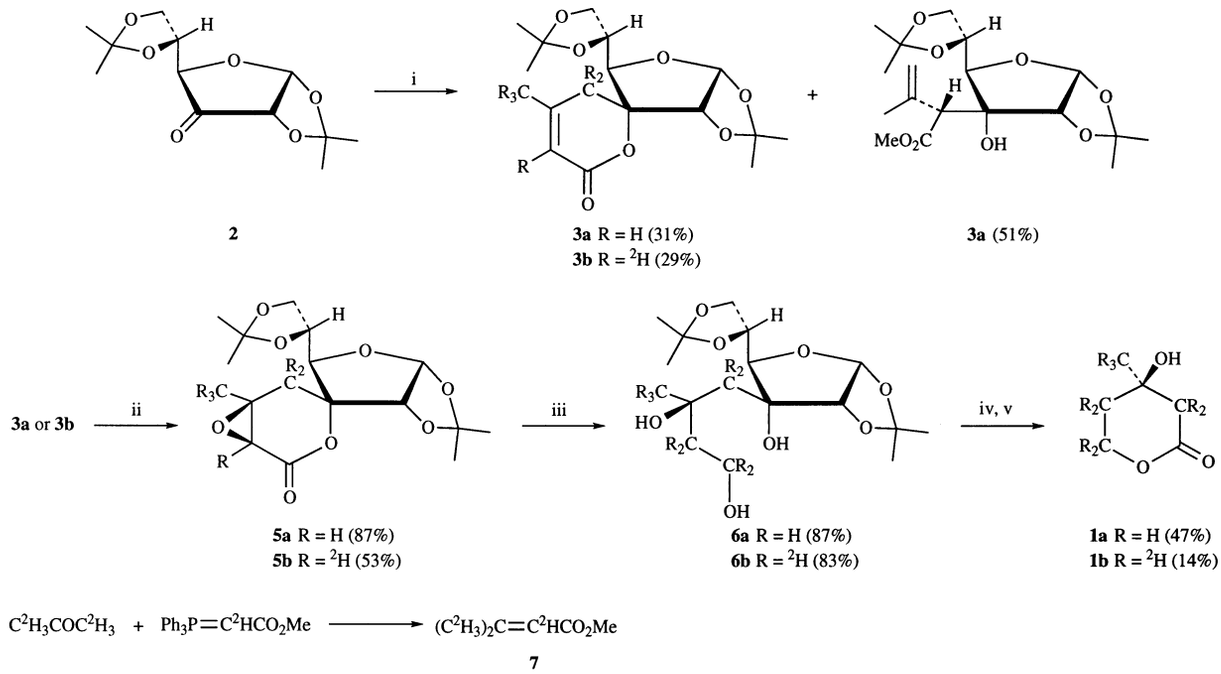
Based on the elucidated transition-state of Overman's allyl imidate rearrangement,[10] together with other stereochemical outcomes of chiral induction on the diacetone-D-glucose template,[11,12] it was envisaged that the diastereotopic face of an olefinic functionality of a spiro-ring implanted on the C-3 of the template could be effectively differentiated by either electrophilic or nucleophilic addition reactions, due to the high steric constraint of the isopropylidene glycol system attached to the C-4β position. Thus, expoxidation of the δ-lactone **3a** under alkaline conditions was expected to afford preferentially the epoxide **5a** with high stereoselection (see Scheme 1).

Results and discussion

We tested this expectation with the key α,β-unsaturated lactone **3a**, which was prepared by addition of an enolate of methyl senecioate to the template ketone, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-ulose, **2**. A major product of this chemistry turned out to be β-hydroxy ester **4** derived from the corresponding α-carbanion, rather than its γ-counterpart. Improvement or alteration of this regiochemistry has been attempted without significant success so far. Although the yield of 28–35% for product **3a** was not high, it was significant in that the desired lactone **3a** could be prepared in a single step.

The crucial step in this synthesis was the subsequent epoxidation of compound **3a**. Before pursuing epoxidation, the preferred or major conformations were analysed with a Monte Carlo conformational search using molecular mechanics calculations.[13] The bicyclo[3.3.0]octane system was shown to be unchanged among the most stable conformers falling within 20 kJ mol^{-1} of the lowest conformational energy. The isopropylidene-glycol substituent on the C-4 of the furanose ring was able to flip in such a way that the glycol system interacts alternately with the δ-lactone in a push-and-pull fashion. In other words, the *Re*-face of the double bond of the lactone was expected to be highly hindered by this interaction from the attack of a hydroperoxide anion. Consequently, stereoselective epoxidation on to the *Si*-face would desirably give rise to a glycidic lactone with 2′*S* configuration. This was actually the case and the diastereoselectivity was significant (*ca.* 18:1 as judged by ^1H NMR spectroscopy of a crude product) in affording, after recrystallization, the desired crystalline epoxide **5a** in 87% yield, which was subsequently subjected to X-ray crystallography to determine its stereochemistry. Thus, the absolute configuration of the epoxide ring was unambiguously assigned as shown in Fig. 1.

Subsequent transformations of the epoxide **5a** were rather straightforward. Simultaneous reduction of the epoxide and the lactone functionalities with $LiAlH_4$ gave a crystalline triol **6a** in 87% yield. The isopropylidene groups were deprotected by acid hydrolysis, and subsequent exhaustive oxidation with $NaIO_4$ gave, without isolation of the intermediary polyol, (*R*)-mevalonolactone **1a** in 47% yield. The synthetic product was identified with (*R*)-mevalonolactone by comparison of ^1H and ^{13}C NMR spectra, mass spectra, as well as optical rotation.[5]



Scheme 1 *Reagents:* i, $(CH_3)_2C{=}CHCO_2Me$, $LiNPr^i_2$ (LDA) or $(C^2H_3)_2C{=}C^2HCO_2Me$ **7**, LDA; ii, H_2O_2, NaOH, MeOH; or H_2O_2, NaOH, MeO^2H; iii, $LiAlH_4$, THF or $LiAl^2H_4$, THF; iv, H^+; v, $NaIO_4$

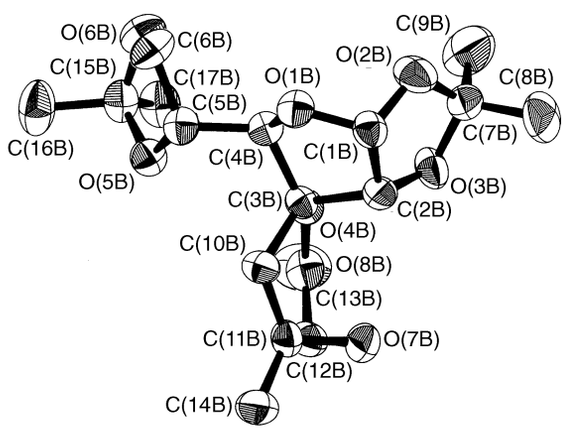


Fig. 1 An ORTEP drawing of compound **5a** showing 30% thermal ellipsoids and crystallographic numbering

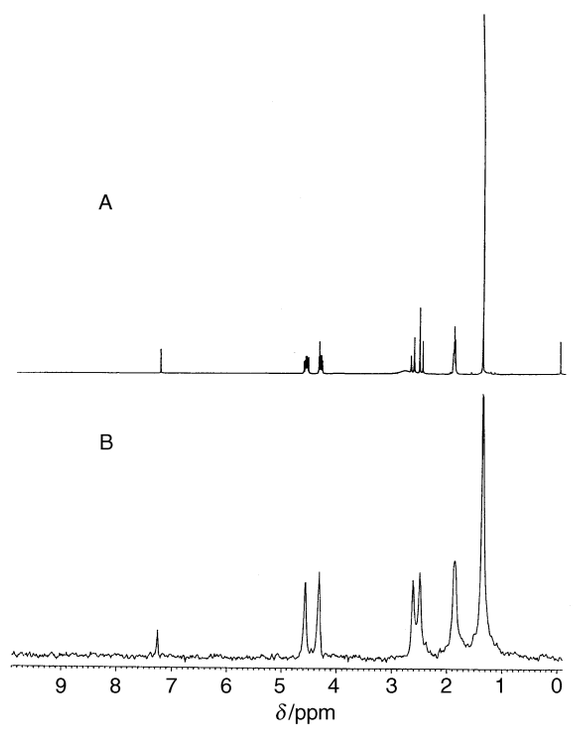


Fig. 2 A; ^{1}H NMR spectrum of (*R*)-mevalonolactone **1a** (300 MHz; C^2HCl_3), B; ^{2}H NMR spectrum of (*R*)-[$^2H_9$]mevalonolactone **1b** (41 MHz; $CHCl_3$)

While the synthetic sequence from the ketone **2** to the final product **1a** has not yet been optimized, the present example afforded lactone **1a** in 11% overall yield in 5 steps.

We then turned our attention to the synthesis of fully deuteriated (*R*)-mevalonolactone. The required [$^2H_7$]senecioate **7** was conveniently synthesized as follow. According to the literature procedure,[14] methoxycarbonylmethylene(triphenyl)-phosphorane was repeatedly treated with ^2H_2O to prepare conveniently the required deuteriated Wittig reagent. Standard Wittig reaction with deuterioacetone in a sealed tube gave the required [$^2H_7$]senecioate **7** in 63% yield. The rest of the synthetic manipulation to afford the fully deuteriated (*R*)-mevalonolactone **1b** was just the same as for the non-deuteriated case. Care was taken in the epoxidation, since the α-methine proton to the carbonyl group was susceptible to an exchange with protium in a protic solvent. By carrying out the reaction in CH_3O^2H, deuterium–protium exchange was reduced to a minimum and the glycidic [$^2H_6$]lactone **5b** was obtained. The high deuterium enrichment of product **5b** was conveniently confirmed with the ^{1}H NMR and mass spectra. Simultaneous reduction was carried out with $LiAl^2H_4$ to yield the [$^2H_9$]triol **6b**. The last step of acidic deprotection and oxidative degradation, as described above, afforded the desired (*R*)-[$^2H_9$]-mevalonolactone **1b**. The ^{2}H NMR spectrum of compound **1b** is shown in Fig. 2. The ^{1}H NMR spectrum showed essentially no significant signal and the ^{13}C NMR spectrum displayed four multiplet signals at δ_C 65.4, 44.0, 34.8 and 28.7, which are split by spin–spin coupling with deuterium. The tertiary alcohol and the carbonyl carbons were observed as singlets at δ_C 67.8 and 170.9, respectively. By looking critically at the ^{13}C NMR spectrum, an additional, weak multiplet was observed at δ_C 44.0 ascribable to C-2. This appeared to be formed by partial protium exchange during the final step of the synthesis.

Although the yields of some steps have not been optimized,

the present synthesis addresses the first and highly enantioselective synthesis of fully deuteriated (*R*)-mevalonolactone. While the first step of the synthesis is not particularly efficient at the moment, the reactions involved are basically easy and convenient. Furthermore, it seems worthwhile to note that the significant diastereoselectivity observed in the epoxidation of compounds **3a**,**b** suggests a general or intrinsic stereochemical tendency in the reactions onto a π-face attached to the C-3 position of the diacetone glucose template system.

With these observations as well as those reported previously, it now appears that the overall steric constraint around the C-3 position of diacetone-glucose is of great significance as an efficient, easily accessible and inexpensive chiral environment. The reactions on this template are principally stereochemically predictable.

Experimental

Mps were measured with a Yanagimoto BY-1 melting point apparatus and are uncorrected. IR Spectra were taken on a Hitachi 285 infrared spectrometer. ^{1}H, ^{2}H and ^{13}C Spectra were recorded on JEOL LA-300 and/or JEOL GSX-500 spectrometers. Deuteriochloroform (99.8% atom enriched, Merck) was used for the NMR solvent throughout, except for the ^{2}H spectrum. ^{1}H, ^{2}H and ^{13}C NMR Chemical shifts are reported in δ units (ppm) based on internal $SiMe_4$ (0 ppm) or solvent signal ($CDCl_3$ δ_D 7.26; $CDCl_3$ δ_C 77.0) as reference. Optical rotations were measured using a JASCO DIP-360 Digital polarimeter, and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a JEOL JMS-AX 505HA spectrometer using a direct inlet system. Column chromatography was carried out with Kieselgel 60 (70–230 mesh, Merck). All reactions were carried out in an inert (Ar or N_2) atmosphere. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl; dimethyl sulfoxide (DMSO) and dichloromethane were distilled from calcium hydride.

α,β-Unsaturated δ-lactone 3a

A solution of butyllithium (1.50 M in hexane; 6.3 cm^3, 9.44 mmol) was added dropwise to a solution of diisopropylamine (1.4 cm^3, 9.8 mmol) in THF (39 cm^3) over a period of 10 min at −78 °C. After being stirred for 25 min at −78 °C, the mixture was warmed to 0 °C and stirring was continued for 1 h at 0 °C. Then the mixture was recooled to −78 °C and a solution of methyl 3-senecioate (methyl 3-methylbut-2-enoate) (1.2 cm^3, 9.4 mmol) in THF (4 cm^3) was added dropwise over a period of 10 min. The mixture was stirred at −78 °C for 1 h, and then at 0 °C for 1.5 h. A solution of ketone **2** (2.0 g, 7.7 mmol) in THF (8 cm^3) was added dropwise over a period of 6 min at 0 °C. After being stirred for 20 min, the reaction mixture was quenched by addition of 1 mol dm^{-3} HCl (6 cm^3) and the mixture was extracted with diethyl ether. The extract was washed successively with 1 mol dm^{-3} HCl (15 cm^3), saturated aq. $NaHCO_3$ (10 cm^3) and brine (15 cm^3), dried over Na_2SO_4, filtered, and concentrated. The residual brown oil (3.4 g) was chromatographed over silica gel with hexane–ethyl acetate (3:1–2:1) to give *lactone* **3a** (802 mg, 31%) and *ester* **4** (1.44 g, 51%).

Compound **3a**; mp 122.8–124.0 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 1727 (C=O) and 1654 (C=C); $[\alpha]_D^{24}$ +167.85 (*c* 0.71, $CHCl_3$); δ_H 5.98 (1 H, s), 5.81 (1 H, d, *J* 4.2), 4.35 (1 H, d, *J* 4.2), 4.23–4.00 (4 H, m), 3.05 (1 H, d, *J* 17.8), 2.08 (3 H, s), 2.05 (1 H, d, *J* 17.8), 1.66 (3 H, s), 1.50 (3 H, s), 1.39 (3 H, s) and 1.38 (3 H, s); δ_C 162.8, 153.7, 118.1, 113.7, 110.1, 103.6, 84.1, 82.5, 80.7, 73.5, 67.8, 32.2, 27.0, 26.6, 26.5, 25.4 and 23.2 (Found: C, 60.28; H, 7.10. $C_{17}H_{24}O_7$ requires C, 59.97; H, 7.11%).

Compound **4**; δ_H 5.55 (1 H, d, *J* 3.8), 5.08 (1 H, s), 5.07 (1 H, s), 4.72 (1 H, s), 4.45 (1 H, d, *J* 3.8), 4.15–4.01 (2 H, m), 3.94 (1 H, d, *J* 9.2), 3.88 (1 H, dd, *J* 4.5 and 7.9), 3.73 (3 H, s), 3.36 (1 H, s, OH), 1.96 (3 H, s), 1.61 (3 H, s), 1.41 (3 H, s), 1.35 (3 H, s) and 1.31 (3 H, s); δ_C 172.1, 139.5, 118.4, 112.8, 109.8, 102.4, 82.3, 82.0, 80.3, 72.9, 68.8, 52.4, 52.0, 26.8, 26.5, 26.3, 25.3 and 21.1 (Found: C, 58.00; H, 7.66. $C_{18}H_{28}O_8$ requires C, 58.03; H, 7.58%).

α,β-Epoxy δ-lactone 5a

A solution of spiro compound **3a** (420 mg, 1.24 mmol) in methanol (1 cm^3) was added to a mixture of 31% aq. H_2O_2 (0.4 cm^3, 4.1 mmol) and 6 mol dm^{-3} NaOH (0.12 cm^3, 0.43 mmol) in methanol (5.4 cm^3) at room temperature. After being stirred for 2.5 h, the reaction mixture was quenched by addition of 1 mol dm^3 HCl (1.5 cm^3) and the mixture was diluted with CH_2Cl_2 (10 cm^3) and water (5 cm^3). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue (476 mg) as a solution in benzene (30 cm^3) was heated for 12 h at reflux with azeotropic removal of water. After removal of the solvent, the residue was purified by chromatography over silica gel with hexane–ethyl acetate (3:1) and recrystallization from hexane–diethyl ether to give compound **5a** (396 mg, 87%) as a crystalline solid, mp 78.5–80.0 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 1742 (C=O); $[\alpha]_D^{28}$ +71.7 (*c* 1.77, $CHCl_3$); δ_H 5.74 (1 H, d, *J* 4.0), 4.73 (1 H, d, *J* 4.0), 4.16–3.94 (4 H, m), 3.45 (1 H, s), 2.63 (1 H, d, *J* 15.1), 2.02 (1 H, d, *J* 15.1), 1.57 (6 H, s), 1.44 (3 H, s), 1.34 (3 H, s) and 1.32 (3 H, s); δ_C 166.4, 113.1, 110.1, 103.6, 83.9 (2 × C), 80.9, 73.5, 67.8, 59.4, 54.4, 29.6, 26.9, 26.7, 26.4, 25.3 and 20.7 (Found: C, 57.50; H, 6.89. $C_{17}H_{24}O_8$ requires C, 57.29; H, 6.79%).

Triol 6a

To a solution of epoxide **5a** (102 mg, 0.29 mmol) in THF (4 cm^3) was addd $LiAlH_4$ (25 mg, 0.63 mmol) and the mixture was stirred for 1 h at room temperature. Water was carefully added and the mixture was diluted with diethyl ether. The insoluble materials were filtered off and washed with diethyl ether. The filtrate and washings were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography over silica gel with diethyl ether to give *triol* **6a** (90 mg, 87%) as a solid, mp 125.2–127.1 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 3500 (OH); $[\alpha]_D^{25}$ +17.92 (*c* 1.04, $CHCl_3$); δ_H 5.73 (1 H, d, *J* 3.5), 4.94 (1 H, d, *J* 3.5), 4.20–4.14 (1 H, m), 4.10 (1 H, dd, *J* 6.0 and 8.3), 3.98–3.83 (4 H, m), 3.76 (1 H, d, *J* 7.5), 3.28 (1 H, s, OH), 3.07 (1 H, br s, OH), 2.21 (1 H, d, *J* 16.0), 2.00 (1 H, ddd, *J* 4.2, 8.4 and 15.2), 1.81 (1 H, ddd, *J* 3,3, 5.8 and 15.2), 1.59 (3 H, s), 1.47 (1 H, d, *J* 16.0), 1.45 (3 H, s), 1.42 (3 H, s) and 1.37 (6 H, s); δ_C 112.6, 109.6, 103.7, 83.5, 81.2, 79.9, 73.9, 73.2, 67.6, 59.6, 43.7, 40.5, 28.8, 26.7, 26.6 (2 × C) and 25.3 (Found: C, 56.62; H, 8.64. $C_{17}H_{30}O_8$ requires C, 56.34; H, 8.34%).

(*R*)-Mevalonolactone 1a

A solution of triol **6a** (108 mg, 0.30 mmol) in 50% aq. trifluoroacetic acid (2 cm^3) was stirred for 2 h at room temperature. The reaction mixture was diluted with water (4 cm^3) and then concentrated to dryness. The residue was dissolved in water (4 cm^3) and $NaIO_4$ (621 mg, 2.91 mmol) was added. The mixture was stirred for 8 h at room temperature. Ethylene glycol (0.12 cm^3) was added, and the mixture was further stirred for 1 h at room temperature. After addition of conc. HCl (0.5 cm^3), the reaction mixture was saturated with NaCl and extracted with $CHCl_3$ (10 cm^3). The aqueous layer was extracted with $CHCl_3$ (10 cm^3 × 20). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography over silica gel with hexane–ethyl acetate (100:1) to give (*R*)-mevalonolactone **1a** (18 mg, 47%) as an oil; $[\alpha]_D^{28}$ −22.6 (*c* 0.528, EtOH) (lit.,[5] −24.0); δ_H 4.61 (1 H, ddd, *J* 5.2, 8.8 and 11.2), 4.35 (1 H, ddd, *J* 4.9, 5.0 and 11.2), 2.77 (1 H, dd, *J* 1.5 and 17.1), 2.52 (1 H, d, *J* 17.1), 1.99–1.90 (2 H, m) and 1.40 (3 H, s); δ_C 170.3, 68.3, 65.9, 44.7, 35.9 and 29.8.

Methyl [$^2H_7$]senecioate 7

To a solution of methyoxycarbonylmethylene(triphenyl)phos-

phorane (56.8 g, 0.17 mol) in CH_2Cl_2 (80 cm^3) was added ^2H_2O (1.48 g, 0.74 mol, 4.3 mol equiv.; 99.8 atom% ^2H, E. Merck) and the mixture was vigorously stirred for 1 h at room temperature. The organic phase was separated, dried over Na_2SO_4, filtrated and concentrated to dryness. This deuterium-exchange sequence was repeated four times to give mono-deuteriated Wittig reagent (52.4 g). A mixture of the reagent (52.4 g) and [$^2H_6$]acetone (10.4 g, 0.16 mol; 99.8 atom% ^2H, E. Merck) in DMSO (40 cm^3) was stirred at 130 °C for 12 h in a sealed tube. After it had cooled to room temperature, distillation of the mixture under reduced pressure gave the title compound **7** (12.6 g, 63%) as a liquid, bp 61–64 °C (55 mmHg); ν_{max}(thin film)/cm^{-1} 2990 (C–H), 2840 (C–H), 2200 (C–^{2}H), 2127 (C–^{2}H), 1740 (C=O) and 1630 (C=C); δ_H 3.68 (3 H, s); δ_C 19.16 (septet, J_{C-D} 19), 26.26 (septet, J_{C-D} 20), 50.59, 115.38 (t, J_{C-D} 25), 156.44 and 167.00.

α,β-Unsaturated [$^2H_6$]δ-lactone 3b

A solution of butyllithium (1.61 M in hexane; 28 cm^3, 0.71 mmol) was added dropwise to a solution of diisopropylamine (7.0 cm^3, 50 mmol) in THF (170 cm^3) over a period of 5 min at −78 °C. After being stirred for 25 min, the mixture was warmed to 0 °C and stirring was continued for 1 h at 0 °C. The mixture was then recooled to −78 °C, and a solution of methyl [$^2H_7$]senecioate **7** (5.47 g, 45.2 mmol) in THF (25 cm^3) was added dropwise over a period of 10 min. The mixture was stirred at −78 °C for 1 h, and then at 0 °C for 1.5 h. To the mixture was added dropwise a solution of ketone **2** (11.7 g, 0.70 mmol) in THF (40 cm^3) over a period of 9 min at 0 °C. After being stirred for 20 min, the reaction mixture was quenched by addition of saturated aq. NH_4Cl and the mixture was extracted with diethyl ether. The extract was washed successively with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated. The residual oil was chromatographed over silica gel with hexane–ethyl acetate (3:1–2:1) to give compound **3b** (1.95 g, 29%) as a solid, mp 134.0–134.8 °C; ν_{max}($CHCl_3$)/cm^{-1} 2220 (C–^{2}H) and 1725 (C=O); $[\alpha]_D^{26}$ +160.2 (*c* 2.03, $CHCl_3$); δ_H 5.77 (1 H, d, *J* 4.2), 4.32 (1 H, d, *J* 4.2), 4.23–4.00 (4 H, m), 1.60 (3 H, s), 1.45 (3 H, s), 1.34 (3 H, s) and 1.33 (3 H, s); δ_C 162.9, 153.6, 117.8 (t, J_{C-D} 26), 113.7, 110.1, 103.6, 84.0, 82.4, 80.6, 73.4, 67.8, 31.4 (quintet, J_{C-D} 18), 26.9, 26.6, 26.5, 25.3 and 22.3 (septet, J_{C-D} 18) (Found: C, 58.93; H, 6.93. $C_{17}H_{18}{}^2H_2O_7$ requires C, 58.95; H, 6.98%).

α,β-Epoxy [$^2H_6$]δ-lactone 5b

A solution of spiro compound **3b** (2.31 g, 6.67 mmol) in methan[^{2}H]ol (30 cm^3) was added to a solution of 31% aq. H_2O_2 (2.3 cm^3) and 6 mol dm^{-3} NaOH (1.1 cm^3) at room temperature. After being stirred for 2 h, the reaction mixture was quenched by addition of 1 mol dm^{-3} HCl (6 cm^3), and the mixture was diluted with diethyl ether (50 cm^3) and water (10 cm^3). The organic layer was separated, and the aqueous layer was further extracted with $CHCl_3$ (15 cm^3 × 10). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue (2.70 g) as a solution in benzene (100 cm^3) was heated for 12 h at reflux with azeotropic removal of water. The solvent was removed under reduced pressure, and then the residue was purified by chromatography over silica gel (3:1 hexane–ethyl acetate) and recrystallization from hexane–diethyl ether to give *compound* **5b** (1.28 g, 53%) as a solid, mp 154.5–155.7 °C; ν_{max}($CHCl_3$)/cm^{-1} 2220 (C–^{2}H) and 1745 (C=O); $[\alpha]_D^{26}$ +67.9 (*c* 4.59, $CHCl_3$); δ_H 5.75 (1 H, d, *J* 4.0), 4.73 (1 H, d, *J* 4.0), 4.16–3.94 (4 H, m), 1.57 (3 H, s), 1.44 (3 H, s), 1.34 (3 H, s) and 1.32 (3 H, s); δ_C 166.4, 113.3, 110.2, 103.7, 83.9 (2 × C), 81.0, 73.6, 68.0, 59.4, 54.0 (t, J_{C-D} 27), 28.8 (quintet, J_{C-D} 19), 26.9, 26.7, 26.5, 25.4 and 20.0 (septet, J_{C-D} 19) (Found: C, 56.65; H, 6.93. $C_{17}H_{18}{}^2H_6O_8$ requires C, 56.35; H, 6.68%).

[$^2H_9$]Triol 6b

A mixtutre of epoxide **5b** (980 mg, 2.7 mmol) and $LiAl^2H_4$ (560 mg, 13 mmol) in THF (20 cm^3) was stirred for 1 h at room temperature. Water was carefully added and the mixture was diluted with diethyl ether. The insoluble materials were filtered off and washed with diethyl ether. The filtrate and washings were combined, dried over Na_2SO_4, filtered and concentrated. The residue was recrystallized from acetone–hexane to give *compound* **6b** (830 mg, 83%) as a solid, mp 120.5–122.0 °C; ν_{max}($CHCl_3$)/cm^{-1} 3500 (OH) and 2225 (C–^{2}H); $[\alpha]_D^{28}$ +15.2 (*c* 2.16, $CHCl_3$); δ_H 5.74 (1 H, d, *J* 3.7), 4.94 (1 H, d, *J* 3.7), 4.20–4.04 (2 H, m), 3.92 (1 H, dd, *J* 3.9 and 8.0), 3.81 (1 H, s, OH), 3.75 (1 H, d, *J* 7.3), 3.22 (1 H, s, OH), 2.88 (1 H, br s, OH), 1.60 (3 H, s), 1.45 (3 H, s), 1.45 (3 H, s) and 1.37 (3 H, s); δ_C 112.5, 109.5, 103.6, 83.3, 81.0, 79.7, 73.4, 73.1, 67.5, 58.7 (quintet, J_{C-D} 22), 42.3 (quintet, J_{C-D} 20), 39.7 (quintet, J_{C-D} 18), 27.8 (septet, J_{C-D} 20), 26.6 (2 × C), 26.5 and 25.2 (Found: C, 55.20; H, 8.35. $C_{17}H_{21}{}^2H_9O_8$ requires C, 54.97; H, 8.14%).

(*R*)-[$^2H_9$]Mevalonolactone 1b

A stirred solution of triol **6b** (660 mg, 1.78 mmol) in 0.1 mol dm^{-3} HCl (16 cm^3) was heated at 100 °C for 20 min. Amberlite IRA-410 resin (OH^- form) was added to the reaction mixture. After filtration, the solution was concentrated under reduced pressure. The residue was dissolved in water (20 cm^3), and $NaIO_4$ (3.90 g, 18.2 mmol) was added. The resulting mixture was stirred for 6 h at room temperature, and ethylene glycol (0.5 cm^3) was added. After stirring of this mixture for 9 h, 1 mol dm^{-3} HCl (1.0 cm^3) was added and the mixture was stirred for 3 h at room temperature. The reaction mixture was saturated with NaCl and extracted with $CHCl_3$ (15 cm^3 × 25). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed over silica gel with hexane–ethyl acetate (3:2) to give (R)-[$^2H_9$]*mevalonolactone* **1b** (34 mg, 14%) as an oil; ν_{max}($CHCl_3$)/cm^{-1} 3420 (OH), 2230 (C–^{2}H) and 1720 (C=O); $[\alpha]_D^{27}$ +23.1 (*c* 0.279, EtOH); δ_C 170.9, 67.8, 65.4 (quintet, J_{C-D} 23), 44.0 (quintet, J_{C-D} 20), 34.8 (quintet, J_{C-D} 20) and 28.7 (septet, J_{C-D} 19); δ_D($CHCl_3$) 4.59 (1 × ^{2}H), 4.30 (1 × ^{2}H), 2.60 (1 × ^{2}H), 2.48 (1 × ^{2}H), 1.82 (2 × ^{2}H) and 1.30 (3 × ^{2}H) (HRMS: found: M^+, 139.1188. $C_6H^2H_9O_3$ requires M, 139.1195).

Crystal-structure determination for compound 5a

A crystal of dimensions 0.45 × 0.30 × 0.20 mm was mounted on a Rigaku RAXIS-IIcs diffractometer equipped with a graphite monochromator, Mo-Kα radiation being used. $C_{17}H_{24}O_8$, M = 356.36, orthorhombic, space group $P2_12_12_1$, a = 12.486(2), b = 17.906(4), c = 16.812(2) Å, V = 3758.7(10) Å^3, F(000) = 1520, Z = 8, D_x = 1.259 Mg m^{-3}, λ = 0.7107, μ = 0.100 mm^{-1}, θ = 1.99–27.76°. The intensity data were measured with 13 imaging plates. A total of 4439 reflections were collected, scaled and averaged from all of the intensity data of 17 155 reflections (R_{int} = 0.0221). The unit-cell parameters were also determined from a least-squares fit with the full reflections. The structure was solved by direct methods using TEXSAN.[15] The refinement was carried out by full-matrix least-squares on F^2 using the SHELXL93 program.[16] The non-hydrogen atoms were refined with anisotropic temperature factors. The hydrogen atoms of five methyl groups were fixed except for rotation around the methyl groups. The positions of the other hydrogen atoms were calculated and not refined. Final R indices were $R(F)$ = 0.0702 for 2248 reflections $F^2 > 2\sigma(F^2)$ and $\omega R(F^2)$ = 0.2035 for all data. There are two crystallographically independent molecules in a unit cell. The structures of the two molecules, A and B, are essentially the same. One of the molecules B is shown in Fig. 1.

Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/84.

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