SYNTHESIS OF (R)-(-)- AND (2R,3R)-(-)-[2-^{2}H]MEVALONOLACTONES

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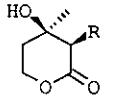
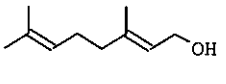
Abstract——Facile synthesis of (R)-(-)- and (2R,3R)-(-)-[2-^{2}H]-mevalonolactones (**1**) from geraniol (**2**) is described.

As a mutual precursor of terpenoides and other natural products having mevalonic acid derived moieties, mevalonolactone (**1a**) has attracted broad interest of chemists and biochemists, and, has been synthesized by a number of approaches.[1] Among those, syntheses of isotopically labeled mevalonates have been contributed to the study of the regio- and stereochemical course of the biosynthesis of mevalonic acid derived natural products.[2,3] We describe in this paper a facile synthesis of (R)-(-)- and (2R,3R)-(-)-[2-^{2}H]mevalonolactones (**1**) from geraniol (**2**).

During the stereochemical investigation of nerol oxide in Bulgarian rose oil, Ohloff *et al*. have synthesized the triol (**3**) from (R)-(-)-linalool (**4**).[4] Although the triol (**3**) has been transformed into (S)-(+)-mevalonolactone, the antipode of the natural mevalonate, **3** has been afforded as a minor product by singlet oxygen oxidation of (R)-(-)-3-hydroxycitronellol (**5**) which has been derived from **4**.[4] In our synthesis of (-)-mevalonolactones (**1**), the allylic alcohols **6** and **7**, were synthesized as key intermediates in regio- and stereoselective manner.



1a: R=H
b: R=D



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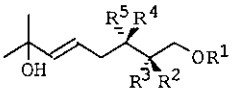
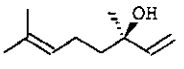


3: R^1=H, R^2=R^3=H, R^4=OH, R^5=CH_3
6: R^1=Bn, R^2=R^3=H, R^4=CH_3, R^5=OH
7: R^1=$C(CH_3)_2O$=R^4, R^2=H, R^3=D, R^5=CH_3



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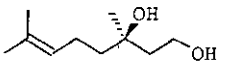

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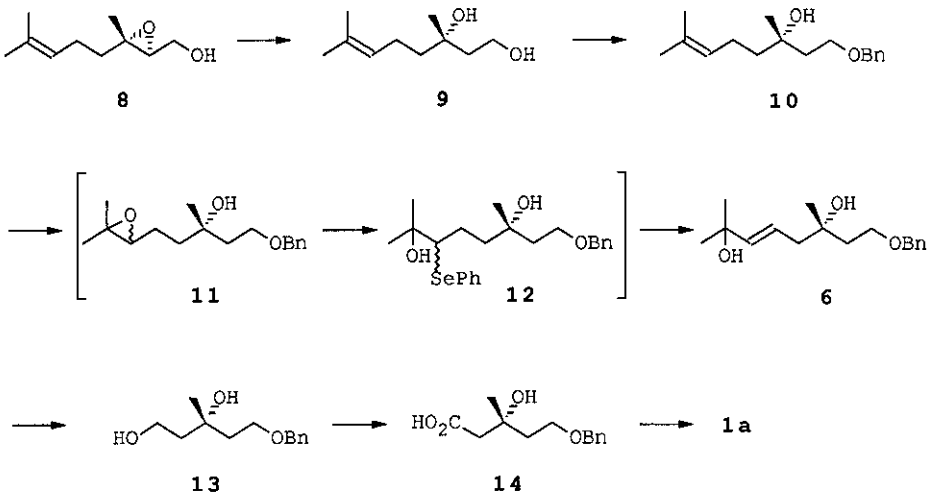
In the synthesis of mevalonolactone, the (2S,3S)-epoxide (**8**) prepared from geraniol (**2**) as reported[5] was first reduced with $LiAlH_4$ to give the 1,3-diol (**9**), $[\alpha]_D^{28}$ -3.0° (c 2.1, $CHCl_3$), in 78% yield. After benzylation of the diol (**9**) giving 92% yield of the 1-O-benzyl ether (**10**) as a sole product, the ether (**10**) was subjected to double bond migration according to the procedure by Sharpless and Laurer.[6] That is, the ether (**10**) was oxidized with m-CPBA to afford the labile epoxide (**11**) which was then treated with $Na(PhSe)BH_3$[6,7] without purification to give **12**. Oxidative elimination of the phenylselenyl substituent in **12** yielded the allylic alcohol (**6**) in 78% from the ether (**10**). Olefinic proton signals were observed at δ 5.62 in the spectrum of the alcohol (**6**). Ozonolysis of the allylic alcohol (**6**) at -78 °C and the following $NaBH_4$ reduction gave 78% yield of the diol (**13**). Jones oxidation of the diol (**13**) afforded 62% of 5-O-benzylmevalonic acid (**14**) which on subsequent hydrogenolysis furnished (R)-(-)-mevalonolactone (**1a**), $[\alpha]_D^{30}$ -18.2° (c 0.65, EtOH) {lit[8] $[\alpha]_D^{20}$ -23° (c 6, EtOH)}, in 70% yield.

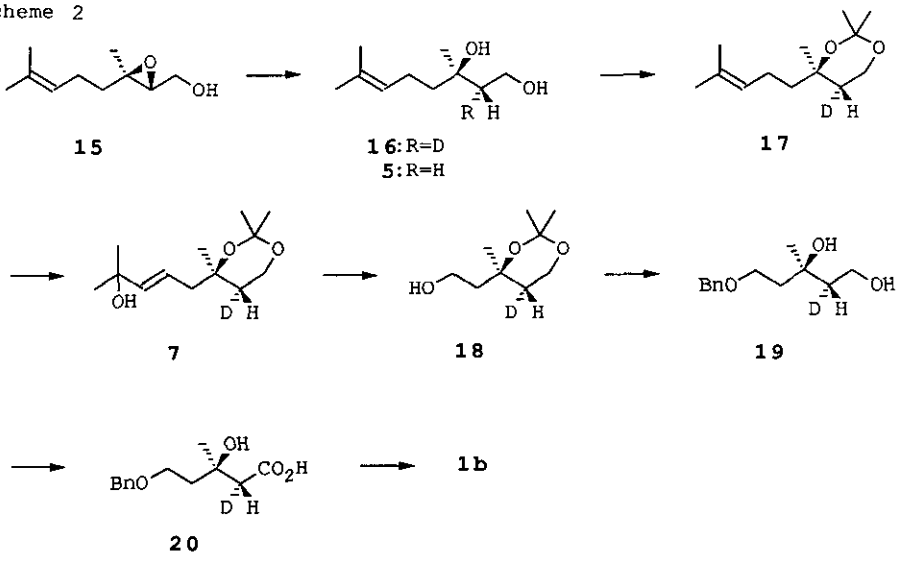
As a labeled mevalonate, we synthesized (2R,3R)-(-)-[2-^{2}H]mevalonolactone (**1b**)[1c] for a stereochemical study of enzymatic reactions.

On reduction with $LiAlD_4$ (98% atom D) the (2R,3R)-epoxide (**15**) gave the deuterated 1,3-diol (**16**), $[\alpha]_D^{28}$ -3.8° (c 1.8, $CHCl_3$), in 72% yield. Optical purity was estimated as ca. 95% e.e. based on the unlabeled 1,3-diol (**5**), $[\alpha]_D^{28}$ -3.8° (c 1.0, $CHCl_3$) {lit[4] $[\alpha]_D^{20}$ -4° (neat)}, which was prepared from **15** by $LiAlH_4$ reduction.

Scheme 1



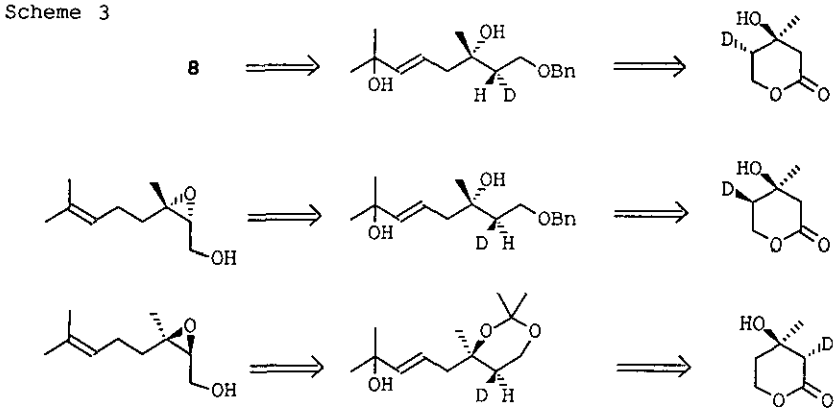
Scheme 2



^1H Nmr spectrum of the diol (**16**) showed 1-methylene signal at δ 3.81 as a doublet. The diol (**16**) was protected as the 1,3-dioxane (**17**, 80% yield) which on subsequent treatment as described above for the benzyl ether (**10**) provided the allylic alcohol (**7**) in 75% yield. The allylic alcohol (**7**) was then ozonized and reduced with $NaBH_4$ to give the primary alcohol (**18**). Since the alcohol (**18**) was somewhat labile on silica gel, **18** was roughly purified and was protected as benzyl ether which was transformed to the diol (**19**) in 30% yield from the allylic alcohol (**7**). Oxidation of the diol (**19**) and the following hydrogenolysis afforded (2R,3R)-(-)-[2-^2H]meval-onolactone (**1b**), $[\alpha]_D^{30}$ -17.1° (c 0.4, EtOH) {lit[1c] $[\alpha]_D$ -19.2° (c 20)}, in 48% yield.

The procedure described above may be applicable to the synthesis of other deuterated mevalonolactones, as illustrated in scheme 3.

Scheme 3



EXPERIMENTAL

^{1}H Nmr (100 MHz) and ^{13}C nmr (25 MHz) were recorded on a JEOL FX-100 spectrometer in $CDCl_3$. Chemical shifts were referred to internal TMS. The other spectral data were obtained on the following spectrometers: Ir on a JASCO A-100S, Ms on a JEOL JMS-01SG-2, and optical rotation on a JASCO DIP-4 Digital Polarimeter.

(S)-3,7-Dimethyl-6-octene-1,3-diol (**9**)

(2S,3S)-2,3-Epoxycitronellol (**8**, 3.05 g, 17.9 mmol) in dry Et_2O (60 ml) was added dropwise to the suspension of $LiAlH_4$ (815 mg, 21.5 mmol) in dry Et_2O (20 ml) and the mixture was refluxed for 2 h. Cooled reaction mixture was quenched with wet Et_2O at 0 °C and the Et_2O layer was washed with 7% $NaHCO_3$ aq., water and sat. NaCl aq., dried and evaporated. To the residue in THF (8 ml) and water (4 ml) was added $NaIO_4$ (766 mg, 3.6 mmol) portionwise and the mixture was stirred at room temperature for 2 h. After adding Et_2O, the mixture was washed with sat. NaCl aq., dried and evaporated. The residue was chromatographed on silica gel (elution with 40-60% EtOAc in hexane) to give the diol (**9**), 2.39 g (78%). $[\alpha]_D^{28}$ +3.0° (c 2.1, $CHCl_3$). FD-ms: m/z 173 (M^+). Ir: ν 3350, 1375 cm^{-1}. ^{1}H Nmr: δ 1.21 (3H, s), 1.59 (3H, s), 1.67 (3H, s), 3.81 (2H, t, J=6 Hz), 5.08 (1H, m). ^{13}C Nmr: δ 17.61 (1C,q), 22.84 (1C, t), 25.71 (1C, q), 26.48 (1C, q), 41.74 (1C, t), 42.39 (1C, t), 42.39 (1C, t), 59.18 (1C, t), 73.27 (1C, s), 124.52 (1C, d), 131.28 (1C, s). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.14; H, 11.96.

(R)-3,7-Dimethyl-6-octene-1,3-diol (**5**)

The (2R,3R)-epoxide (**15**, 2.58 g, 15.1 mmol) was treated as above using $LiAlH_4$ (635 mg, 16.7 mmol) to give the diol (**5**), 1.82 g (70%). $[\alpha]_D^{28}$ -3.8° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.26; H, 11.96.

(2S,3R)-3,7-Dimethyl-[2-^{2}H]-6-octene-1,3-diol (**16**)

Following the above procedure, the (2R,3R)-epoxide (**15**, 1.97 g, 11.6 mmol) was reduced with $LiAlD_4$ (98% atom D, 487 mg, 11.6 mmol) to give the diol (**16**), 1.43 g (72%). $[\alpha]_D^{28}$ -3.8° (c 1.8, $CHCl_3$). FD-ms: m/z 174 (M^+). Ir: ν 3350, 1375 cm^{-1}. ^{1}H Nmr ($CDCl_3$+D_2O): δ 1.22 (3H, s), 1.60 (3H, s), 1.67 (3H, s), 3.81 (2H, d, J=5.5 Hz), 5.09 (1H, m). ^{13}C Nmr: δ 17.61 (1C, q), 22.72 (1C, t), 25.66 (1C, q), 26.48 (1C, q), 41.16 (1C, m), 42.33 (1C, t), 59.36 (1C, t), 73.51 (1C, s), 124.29 (1C, d), 131.57 (1C, s). Anal. Calcd for $C_{10}H_{19}DO_2$: C, 69.32; H, 11.1. Found: C, 68.64; H, 12.20.

(S)-1-Benzyloxy-3,7-dimethyl-6-octen-3-ol (**10**)

To the mixture of the diol (**9**, 110 mg, 0.64 mmol) in dry DMF (1 ml) was added 60% NaH (31 mg, 0.77 mmol) at 0 °C and the mixture was stirred for 30 min. Benzyl bromide (0.92 µl, 0.77 mmol) was added to the above mixture and the whole was stirred at room temperature overnight. The reaction mixture was diluted with Et_2O (20 ml), washed with water and sat. NaCl aq., dried and evaporated. Silica gel chromatography (10% Et_2O in hexane elution) of the residue gave the alcohol (**10**), 155 mg (92%). FD-ms: m/z 262 (M^+). Ir: ν3460, 1370 cm^{-1}. ^1H Nmr: δ 1.18 (3H, s), 1.59 (3H, s), 1.67 (3H, s), 3.14 (1H, s), 3.69 (2H, t, J=6 Hz), 4.49 (2H, s), 5.08 (1H, t, J=4 Hz), 7.29 (5H, s). ^{13}C Nmr: δ 17.55 (1C, q), 22.72 (1C, t), 25.66 (1C, q), 26.54 (1C, q), 39.81 (1C, t), 42.21 (1C, t), 67.40 (1C, t), 72.21 (1C, s), 73.33 (1C, t), 124.52 (1C, d), 127.64 (3C, d), 128.34 (2C, d), 131.22 (1C, s), 137.73 (1C, s).

(S)-8-Benzyloxy-2,6-dimethyl-3-octene-2,6-diol (**6**)

To the alcohol (**10**, 1.06 g, 4.04 mmol) in hexane (40 ml) and 7% $NaHCO_3$ aq. (18 ml) was added m-CPBA (1.05 g, 4.85 mmol) portionwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h, cooled to 5-10 °C and filtered. The filtered organic phase was washed with cold 1N NH_4OH, 15% NaCl and sat. NaCl aq., dried and evaporated. Crude epoxide in abs EtOH (50 ml) was added to the EtOH solution of phenylselenyl anion prepared from PhSeSePh (843 mg, 2.70 mmol) and $NaBH_4$ (204 mg, 5.40 mmol) in abs EtOH (35 ml).[6] The reaction mixture was refluxed for 2 h under stirring, diluted with THF (65 ml) and cooled to -15 °C. After adding pyridine (5.6 ml), 30% H_2O_2 (4.6 ml) in THF (5 ml) was added dropwise to the above solution during the period of 2 h. The mixture was stirred at 0 °C overnight and at room temperature for 3 h. Dilution with Et_2O (130 ml) was followed by washing with 15% NaCl and sat. NaCl aq. Dried organic phase was evaporated and subjected to silica gel chromatography. Elution with 25% EtOAc in hexane gave the diol (**6**), 878 mg (78%). FD-ms: m/z 279 (M^+). Ir ν: 3390, 1370 cm^{-1}. ^1H Nmr: δ 1.16 (3H, s), 1.28 (2X3H, s), 3.68 (2H, t, J=6 Hz), 4.48 (2H, s), 5.62 (2H, m), 7.29 (5H, s). ^{13}C Nmr: δ 26.65 (1C, q), 29.77 (2C, q), 39.75 (1C, t), 45.09 (1C, t), 67.34 (1C, t), 70.51 (1C, s), 72.27 (1C, s), 73.39 (1C, t) 122.29 (2C, d), 127.69 (2C, d), 128.40 (2C, d), 137.73 (1C, s), 141.67 (1C, d).

(S)-5-Benzyloxy-3-methylpentane-1,3-diol (**13**)

The diol (**6**, 933 mg, 3.57 mmol) in MeOH (60 ml) and pyridine (1.8 ml) was ozonized at -78 °C. Excess of O_3 was removed and $NaBH_4$ (670 mg, 17.9 mmol) was added

portionwise to the mixture. This was allowed to stand at room temperature for 36 h and evaporated under reduced pressure. The reaction mixture was taken up with Et_2O and water, and the Et_2O layer was washed with 10% citric acid, water and sat. NaCl aq., dried and evaporated. Silica gel chromatography (50% EtOAc in hexane elution) of the residue yielded the diol (**13**), 878 mg (78%). $[\alpha]_D^{30}$ -6.4° (c 1.1, $CHCl_3$). FD-ms: m/z 225 (M^+). Ir: ν 3400, 1379, 1100 cm^{-1}. ^1H Nmr: δ 1.25 (3H, s), 3.5-4.0 (4H, m), 4.49 (2H, s), ^{13}C Nmr: δ 26.54 (1C, q), 40.39 (1C, t), 42.33 (1C, t), 59.47 (1C, t), 67.22 (1C, t), 73.45 (1C, t), 73.62 (1H, s), 127.60 (2C, d), 127.81 (1C, d), 128.46 (2C, d), 135.56 (1C, s).

(R)-5-O-Benzylmevalonic acid (**14**)

The diol (**13**, 83 mg, 0.37 mmol) in acetone (15 ml) was treated with 8N Jones' reagent (0.14 ml, 1.11 mmol) for 30 min. The reaction mixture was quenched with ^iPrOH, diluted with EtOAc and washed with water and sat. NaCl aq., dried and evaporated. The residue was dissolved in Et_2O (30 ml) and extracted with 0.5N NH_4OH (2 X 0.5 ml) and with water (0.5 ml). The water layer was washed with Et_2O, acidified with citric acid and re-extracted with Et_2O. Et_2O layer was washed with sat. NaCl aq., dried and evaporated. The residue was chromatographed on silica gel (40% Et_2O in hexane elution) to give the acid (**14**), 55 mg (62%). FD-ms: m/z 239 (M^+). Ir: ν 3400, 1705, 1370, 1100 cm^{-1}. ^1H Nmr: δ 1.30 (3H, s), 2.45 (1H, d, J=16 Hz), 2.62 (1H, d, J=16 Hz), 3.69 (2H, t, J=6 Hz), 4.49 (2H, s), 7.29 (5H, s). ^{13}C Nmr: δ 26.77 (1C, q), 39.57 (1C, t) 45.62 (1C, t), 66.87 (1C, t), 71.45 (1C, s), 73.51 (1C, t), 127.81 (2C, d), 127.99 (1C, d), 128.52 (2C, d), 137.27 (1C, s), 174.72 (1C, s).

(R)-Mevalonolactone (**1a**)

The acid (**14**, 55 mg, 0.23 mmol) in EtOH (2 ml) was hydrogenolyzed with 5% Pd-C (15 mg) as a catalyst. After filtration through Celite pad and evaporation, the residue was chromatographed on silica gel (50% EtOAc in benzene elution) to give the lactone (**1a**), 21 mg (70%). $[\alpha]_D^{30}$ -18.2° (c 0.65, EtOH). Ms: m/z 130.0631 (M^+, Calcd 130.0629 for $C_6H_{10}O_3$). Ir: ν 3410, 1725 cm^{-1}. ^1H Nmr: δ 1.39 (3H, s), 1.90 (2H, m), 2.58 (2H, m),4.2-4.8 (2H, m).

(4R,5S)-4-(4-Methyl-3-pentenyl)-2,2,4-trimethyl-[5-^2H]-1,3-dioxane (**17**)

The mixture of the diol (**16**, 1.31 g, 7.6 mmol), 2,2-dimethoxypropane (5 ml), pyridinium p-toluenesulfonate (PPTS, 251 mg, 1.0 mmol) in dry CH_2Cl_2 (3 ml) was stirred at room temperature for 1.5 days. The reaction mixture was concentrated under reduced pressure, diluted with Et_2O, washed with sat. NaCl aq., dried and evapo-

rated. Silica gel chromatography (10% Et_2O in hexane elution) of the residue gave the acetal (**17**), 1.27 g (79%). Ms: m/z 213 (M^+). Ir: ν 1195 cm^{-1}. ^1H Nmr: δ 1.27 (3H, s), 1.39 (3H, s), 1.41 (3H, s), 1.60 (3H, s), 1.67 (3H, s), 3.88 (2H, m), 5.08 (1H, m), ^{13}C Nmr: δ 17.55 (1C,q), 22.19 (1C, t), 25.66 (1C, q), 27.36 (2C, q), 33.47 (1C, m), 43.27 (1C, t), 56.60 (1C, t), 72.10 (1C, s), 97.69 (1C, s), 124.58 (1C, d), 131.10 (1C,s).

(4R,5S)-4-(4-Hydroxy-4-methyl-2-pentenyl)-2,2,4-trimethyl-[5-^2H]-1,3-dioxane (**7**)

Following the procedure for **6**, the acetal (**17**, 579 mg, 2.7 mmol) gave the allylic alcohol (**7**), 462 mg (75%). FD-ms: m/z 230 (M^+). Ir: ν 3420, 1375, 1195 cm^{-1}. ^1H Nmr: δ 1.25 (3H, s), 1.31 (2X3H, s), 1.38 (3H, s), 1.42 (3H, s), 3.89 (2H, m), 5.62 (2H, m). ^{13}C Nmr: δ 27.07 (1C, q), 27.36 (1C, q), 29.12 (1C, q), 29.77 (2C, q), 32.76 (1C, m), 46.03 (1C, t), 56.48 (1C, t), 70.51 (1C, s), 72.33 (1C, s), 97.93 (1C, s), 122.12 (1C, d), 141.49 (1C, d).

(2S,3R)-5-Benzyloxy-3-methylpentane-[2-^2H]-1,3-diol (**19**)

The allylic alcohol (**7**, 284 mg, 1.24 mmol) in MeOH (30 ml) was ozonized at -30 °C. $NaBH_4$ (477 mg, 12.6 mmol) was added to the O_3 free mixture portionwise and the mixture was stirred at ambient temperature for 1 h. Concentrated mixture was diluted with EtOAc and passed through alumina column. The filtrate was chromatographed on silica gel (25% EtOAc in hexane elution) to give the alcohol (**18**), 97 mg. To the alcohol (**18**, 97 mg, 0.55 mmol) in dry DMF (2 ml) was added 60% NaH (27 mg, 0.66 mmol) at 0 °C. After 30 min of stirring, benzyl bromide (800 μl, 0.66 mmol) was added to the mixture and the whole was stirred overnight at room temperature. The reaction mixture was diluted with Et_2O (20 ml), washed with water and sat. NaCl aq., dried and evaporated. The residue and PPTS (30 mg, 0.12 mmol) in MeOH (10 ml) was refluxed for 2 h and evaporated. Silica gel chromatography (50-60% EtOAc in hexane elution) of the residue gave the diol (**19**), 84 mg (30%). FD-ms: 226 (M^+). Ir: ν 3350, 1370, 1090 cm^{-1}. ^1H Nmr ($CDCl_3$+D_2O): δ 1.25 (3H, s), 3.7-4.0 (4H, m), 4.50 (2H, s), 7.29 (5H, s). ^{13}C Nmr: δ 26.54 (1C, q), 40.39 (1C, t), 41.98 (1C, m), 59.24 (1C, t), 67.11 (1C, t), 73.33 (2C, t), 127.64 (3C, d), 128.34 (2C, d), 137.62 (1C, s).

(R)-5-O-Benzyl-[2-^2H]mevalonic acid (**20**)

Following the procedure for **14**, the diol (**19**, 77 mg, 0.34 mmol) gave the acid (**19**), 59 mg (72%). Ms: m/z 239 (M^+). Ir: ν 3370, 1700, 1370, 1100 cm^{-1}. ^1H Nmr: δ 1.31 (3H, s), 1.90 (2H, m), 2.56 (1H, s), 3.70 (2H, t, J=6 Hz), 4.49 (2H, s), 7.29 (5H, s).

(2R,3R)-[2-^{2}H]Mevalonolactone (**1b**)

Hydrogenolysis of the acid (**20**, 49 mg, 0.21 mmol) by the procedure for **1a** afforded the lactone (**1b**), 18 mg (67%). $[\alpha]_D^{30}$ -17.1° (c 0.4, EtOH). Ms: m/z 131.0690 (M^+, Calcd 131.0692 for $C_6H_9DO_3$). Ir: ν 3420, 1720 cm^{-1}. ^{1}H Nmr: 1.39 (3H, s), 1.8-2.0 (2H, m), 2.49 (1H, t, J=3 Hz), 4.2-4.8 (2H, m).

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