Facile and Highly Effective Synthesis of (-)-Mevalonic-2-*d* and -4-*d* Acid Lactones

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Monodeuterated mevalonic acid lactones, 2*R*,3*R*-2-*d*, 2*S*,3*R*-2-*d*, 3*S*,4*R*-4-*d*, and 3*S*,4*S*-4-*d*, **1**–**4**, which are useful tools for terpenoid biosynthetic studies, were synthesized via a short and efficient route in 42–48% yields from 3-butyn-1-ol.

The feeding of stereoselectively labelled mevalonic acid lactones (MVA, **1**–**4**) to enzyme systems is a useful tool for the elucidation of the stereochemistry of enzymatic reactions.[1] During the course of our work on the biosynthesis of sweet potato phytoalexins,[2] we required multigram quantities of **1** and **2**. The classical methodology of Cornforth[3] and Popjak yields racemic **1**, **2**, **3**, and **4** in 1.3, 2.5, 3.2, and 6.2% overall yield, respectively. We report here a much improved and convenient synthesis of **1**–**4** bearing the natural configuration at C-3 (see Scheme I).

Ethoxyethylation of 3-butyn-1-ol **5** followed by carboethoxylation of the lithium salt of **6** gave the acetylenic ester **7** in 88% yield. Conjugate addition of (dimethylcopper)lithium followed by quenching with deuterium oxide furnished the *Z* unsaturated ester **8** with 50:1[4] stereoselectivity (97% incorporation of *d*). Reduction of **8** with $LiAlH_4$ gave the allylic alcohol **9**. Epoxidation by Sharpless' method [5] using (+)-diethyl tartrate yielded the 2*S*,3*R*-epoxy alcohol **10**, which was reduced with $LiAlH_4$ to the 2*S*,3*R*-diol **11** (83% yield after flash chromatography).[6] Oxidation of **11** with alkaline potassium permanganate proceeded smoothly to give a solution of protected mevalonate, which was acidified to effect hydrolysis of the ethoxyethyl group. Interestingly, workup afforded us a mixture of **1** and free mevalonic acid. Complete lactonization was achieved with *p*-toluenesulfonic acid to give a highly hygroscopic (2*R*,3*R*)-MVA-2-*d* (**1**) in 85% yield. The diastereomeric (2*S*,3*R*)-MVA-2-*d* (**2**) was obtained in an analogous manner, except that H_2O was used in quenching the methyl cuprate addition product of **7** and $LiAlD_4$ was used in the reduction of **16** to **17**.

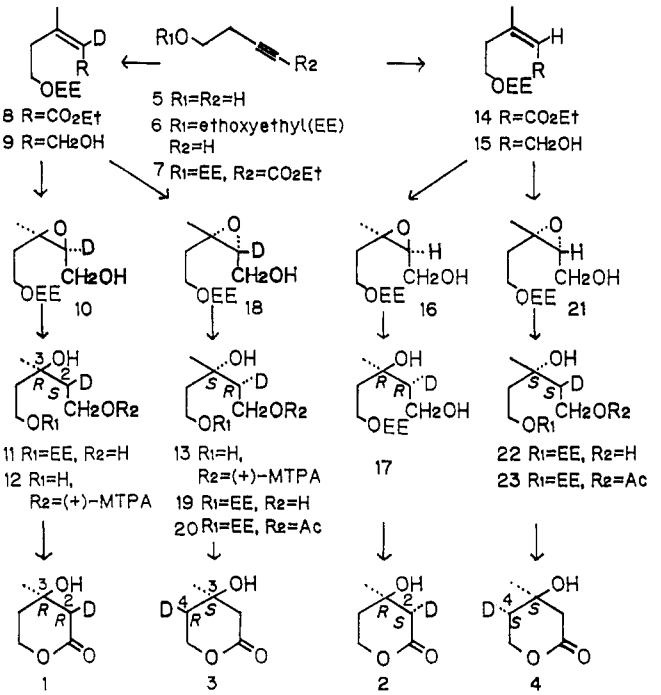
Optical purity of **10** was determined via the (+)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA)[7] ester **12**. Comparison of the C-3 methyl resonances (^1H NMR) with an authentic mixture [8] of MTPA esters **12** (δ 1.24 ppm) and **13** (δ 1.23 ppm) showed **12** to contain 4% of **13** (92% enantiomer excess).

In the preparation of the (3*S*,4*R*)-MVA-4-*d* **3**,[9] olefin **9** was epoxidized using unnatural (-)-diethyl tartrate to give 2*R*,3*S*-epoxy alcohol **18**. Reduction of **18** to the 2*R*,3*S*-diol **19**, followed by selective acetylation of the primary alcohol yielded **20**. After removal of the ethoxyethyl group, Jones oxidation[10] of the resulting alcohol followed by hydrolysis of the acetyl group and acid-catalyzed lactonization yielded **3** in 74%. (3*S*,4*S*)-MVA-4-*d* (**4**) was prepared from **15** in the same manner as **9** to **3** except that $LiAlD_4$ was employed in the reduction of **21** to **22**.

The relative stereochemistry of deuterium in **1**–**4** can be verified by inspection of the 360-MHz ^1H NMR spectra. Lactone **1** exhibits a clear triplet for 2-H (J = 3 Hz) due to H–D coupling (Figure 1a). The poorly resolved pattern for 2-H in lactone **2** (due to W coupling with 4α-H in addition to H–D coupling) indicates that 2-H is equatorial (Figure 1b). In lactone **1** the absence of long-range coupling to H-2 is consistent with its axial orientation. The axial proton 5α-H in **3** has large axial–axial ($J_{5\alpha4\beta}$ = 13 Hz) and large geminal ($J_{5\alpha5\beta}$ = 13 Hz) coupling, but lacks any axial–equatorial coupling, demonstrating the C-4 deuteron is equatorially oriented (Figure 1c). In isomer **4** $J_{5\alpha4\beta}$ is replaced with axial–equatorial coupling ($J_{5\alpha4\alpha}$ = 3.5 Hz) in accordance with an axially disposed deuteron at C-4 (Figure 1d).

The overall yields of **1**, **2**, **3**, and **4** from commercially available **5** were 50.0, 44.0, 42.5, and 42.0%, respectively

Scheme I



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(1) For a review on the use of deuterated and tritiated mevalonates in biosynthetic studies see: Schutte, H. R.; Stock, M. *Isotopenpraxis* **1979**, *15*, 197. Generally, the salts of the hydroxy acids are used in incorporation experiments.

(2) Schneider J. A.; Lee J.; Yoshihara K.; Mizukawa K.; Nakanishi K. *J. Chem. Soc., Chem. Commun.* **1984**, 372.

(3) Cornforth R. H.; Popjak G. In "Methods in Enzymology"; Colowick, S. P., Kaplan, N. O., Eds.); Academic Press: New York 1969; Vol. 15, pp 369.

(4) Siddal, L. B.; Biskup, M.; Fried, J. H. *J. Am. Chem. Soc.*, **1969**, *91*, 1853.

(5) Katsuki, T.; Sharpless, K. *J. Am. Chem. Soc.* **1980**, *102*, 5976.

(6) Still, W. C.; Kahn M.; Mitra A. *J. Org. Chem.* **1978**, *43*, 2943.

(7) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(8) Obtained from racemic **10** (see Experimental Section).

(9) The 3*S* configuraion of MVA-4-d_1 corresponds to the natural 3*R* configuration of MVA.

(10) Bowden, K.; Heilbron, I. M.; Jones, E. H. R.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

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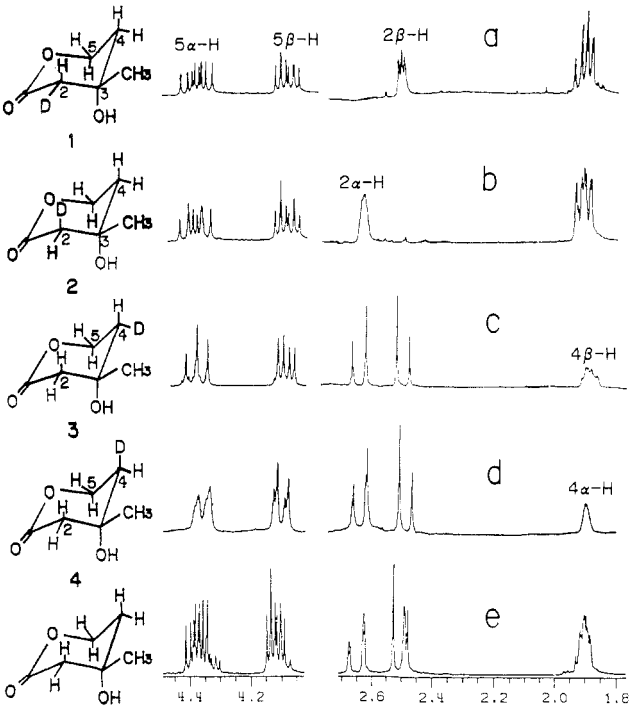

Figure 1. ^{1}H NMR spectra (360 MHz) of (a) 2*R*,3*R*-MVA-2-*d*, (1), (b) 2*S*,3*R*-MVA-2-*d* (**2**) (c) 3*S*,4*R*-MVA-4-*d* (**3**), (d) 3*S*,4*S*-MVA-4-*d* (4), and (e) unlabelled MVA.

(with optical purities of 91.2, 89.3, 90.0, and 81.0%, respectively).[11] Attempts to improve the optical purity by modifying the epoxidation conditions were not successful. Contamination by the enantiomeric lactones is of little consequence as only the material with the natural C-3 configuration is incorporated into terpenoids.[3]

Since most reaction times are short and the sequence is efficient, 1 g of **5** yields approximately 1 g of labeled MVA. Also large-scale work is not necessary. Furthermore, if one is content with racemic forms of **1**–**4**, *m*-chloroperbenzoic acid oxidation of esters **8** and **14**[12] (or the alcohols **9** and **15**) makes the sequence even simpler and more rapid. Usage of $LiAlT_4$ and T_2O in the scheme should lead to the tritiated lactones. We anticipate that the ready availability of stereospecifically labelled optical active MVAs **1**–**4** will facilitate and encourage further biosynthetic experiments.

Experimental Section

Rotations were determined in methanol. Moisture-sensitive reactions were carried out in flame-dried glassware under nitrogen. Tetrahydrofuran (THF) and ether were distilled from $LiAlH_4$; other solvents such as CH_2Cl_2 were not further purified.

3-Butynyl Ethoxyethyl Ether (6). To 30 ml of ethyl vinyl ether (freshly distilled) containing *p*-toluenesulfonic acid (50 mg) was added 3-butyn-1-ol (7 g, 0.1 mol) dropwise at 0 °C. After 20 min, the reaction mixture was warmed to room temperature, and diluted with 100 mL of hexane. Filtration through basic alumina and concentration gave a colorless oil **6** (13.3 g, 0.094 mol, 94%): IR ν 3300, 2130 (C≡C), 1390, 1120 cm^{-1}; ^{1}H NMR δ 4.70 (q, 1 H, J = 7 Hz), 3.28 (m, 4 H), 2.42 (dt, 1 H, J = 2 and 7 Hz), 1.94 (t, 1 H, J = 2 Hz), 1.29 (d, 3 H, J = 7 Hz)), 1.17 (t, 3 H, J = 7 Hz).

Ethyl 5-(2-Ethoxyethoxy)pent-2-ynoate (7). Under anhydrous conditions, a three-neck flask containing 70 mL of dry THF was charged with **6** (6.11 g, 43.0 mmol) and chilled to −78°. One equivalent (25.3 mL) of *n*-butyllithium (1.7 M in hexane) was added dropwise. After 10 min, ethyl chloroformate (5.43 g, 50 mmol) in 25 mL of THF was added, followed by addition of tetramethylenediamine (6.7 mL, 44 mmol) in 25 mL of THF. After stirring for 15 min, the reaction was warmed to room temperature, filtered through Florisil, and concentrated, and kugelrohr distillation (1 torr, 150 °C) yielded **7** (8.19 g, 38.3 mmol, 91%): MS, m/z 214 (0.8%), 199 (38%), 139 (100%); IR ν = 2240 (C≡C), 1710 cm^{-1} (C=O); ^{1}H NMR δ = 4.63 (q, 1 H, J = 7 Hz), 4.10 (q, 2 H, J = 7 Hz), 3.65–3.30 (m, 4 H), 2.48 (t, 2 H, J = 7 Hz), 1.20 (d, 3 H, J = 7 Hz), 1.18 (t, 3 H, J = 7 Hz), 1.09 (t, 3 H, J = 7 Hz).

(*Z*)-Ethyl 5-(2-Ethoxyethoxy)-3-methyl-2-pentenoate-*2*-*d* (8). In a slight variation of the reported procedure[4] CuI (2.0 g, 10.5 mmol) was suspended in 50 ml of dry ether at 0 °C. Ethereal methyllithium (1.5 M) was added until almost all of the yellow methylcopper reacted (13.5 ml). After, chilling to −78 °C **7** (2.01 g, 9.39 mmol) in 50 mL of ether was rapidly added. Stirring was continued for 5 min, then 3 mL of D_2O was added. After warming to ambient temperature, the reaction mixture was filtered through Florisil and washed with 150 mL of ether. Concentration under reduced pressure afforded **8** (2.06 g, 9.00 mmol, 96%); 97% *d*, *Z*:*E* = 50:1; MS/ m/z 201 (M$^+$ − C=O, 1.1%), 142 (32%), 114 (30%), 73 (100%); IR ν 2240 (C–D), 1710 (C=O), 1640 cm^{-1} (C=C); ^{1}H NMR δ 5.71 (bs, 0.03 H, trace of undeuterated olefin proton), 4.67 (q, 1 H, J = 7 Hz), 4.12 (q, 2 H, J = 7 Hz), 3.75–3.40 (m, 4 H), 2.88 (t, 2 H, J = 7 Hz), 2.14 (s, 0.06 H, 2% of *E* isomer), 1.94 (s, 3 H), 1.27 (d, 3 H, J = 7 Hz), 1.25 (t, 3 H, J = 7 Hz), 1.17 (t, 3 H, J = 7 Hz).

5-(2-Ethoxyethoxy)-3-methyl-2-penten-1-ol-*2*-*d* (9). To a suspension of $LiAlH_4$ (340 mg, 8.9 mmol) in 20 mL of ether was added **8** (3.53 g, 15.4 mmol) in 5 ml of ether at 0 °C. After 20 min the reaction was quenched by the sequential addition of 0.5 mL of H_2O, 0.5 mL of 15% NaOH, and 1.5 mL of H_2O. The solution was filtered through Celite and washed with 100 mL of ethyl acetate (AcOEt). Evaporation of the solvent gave a residue which was flash chromatographed with hexane–AcOEt (3:1) to yield pure **9** (2.60 g, 13.8 mmol, 89%): MS, m/z = 143 (M$^+$ − CH_3CH_2OH, 1%), 73 (M$^+$ − $CH_3CH_2OCHCH_3$, 100%); IR ν 3400 (O–H), 2235 (C–D), 1650 (C=C), 1130 cm^{-1}; ^{1}H NMR δ 4.66 (q, 1 H, J = 7 Hz), 3.98 (bs, 2 H), 3.66–3.39 (m, 4 H), 2.34 (t, 2 H, J = 7 Hz), 1.74 (s, 3 H), 1.27 (d, 3 H, J = 7 Hz), 1.16 (t, 3 H, J = 7 Hz), 5.71 (t, 0.03 H, trace amount of undeuterized olefin proton).

(2*S*,3*R*)-5-(2-Ethoxyethoxy)-3-methylpentane-1,3-diol-*2*-*d* (11). Allylic alcohol **9** (1.88 g, 9.95 mmol), titanium tetraisopropoxide (2.97 mL), (+)-diethyl tartrate (1.72 mL), and anhydrous *tert*-butyl hydroperoxide (3.3 M, 6.25 mL) were allowed to react according to the literature[5] procedure. The crude product was filtered through SiO_2 (hexane–EtOAc, 7:3) to give **10** contaminated with diethyl tartrate. This material (1.76 g) was dissolved in 5 mL of ether and added to a suspension of $LiAlH_4$ (130 mg, 3.4 mmol) in 25 mL of ether at 0 °C. After stirring for 30 min, the reaction was quenched by the sequential addition of 0.3 mL of H_2O, 0.3 mL of 15% NaOH, and 1.0 mL of H_2O. Filtration through Celite, concentration, and flash chroamtography with hexane–AcOEt (1:1) yielded pure **11** (1.70 g, 8.3 mmol, 83%): $[\alpha]_D$ −2.8° (*c* 20); MS, m/z 162 (M$^+$ −OCH_2CH_3, 1.5%), 146 (8%), 115 (30%), 100 (35%), 73 (100%). IR ν 3400 (O–H), 2180 (C–D), 1380, 1130, 940 cm^{-1}; ^{1}H NMR δ 4.68 (q, 1 H, J = 7 Hz), 3.95–3.38 (m, 6 H and 2 OH), 1.92 (m, 1 H), 1.78 (m, 1 H), 1.67 (m, 1 H), 1.30 (d, 3 H, J = 7 Hz), 1.27 (d, 3 H), 1.19 (t, 3 H, J = 7 Hz).

1-(+)-MTPA Ester of (2*S*,3*R*)-3-Methylpentane-1,3,5-triol-*2*-*d* (12). Diol 11 (3 mg) was treated with triethylamine (1 drop) and (+)-MTPA chloride (10 mg) in CH_2Cl_2 (0.1 mL) for 30 min. After dilution with hexane (0.5 mL), filtration, and concentration, the crude product was treated with 1 drop of 0.1 N HCl in 2 mL methanol for 1 h to hydrolyze the ethoxyethyl group. After addition of triethylamine (1 drop) and concentration, the residue was flash chromatographed (hexane:AcOEt = 1:1) to afford a sample of pure dihydroxy ester **12**: MS, m/z 274 (10%, M$^+$ − C_6H_5), 189 (100%, MTP − methyl); IR ν 3400 (O–H), 2170 (C–D), 1740 (C=O), 1270, 1020, 920 cm^{-1}; ^{1}H NMR δ 7.55–7.38 (m, 5 H), 4.49 (m, 2 H), 3.87 (m, 2 H), 3.55 (s, 3 H), 2.80 (bs, OH)

(11) Determined by comparison to the optical rotation of undeuterated MVA: Cornforth, R. H.; Popjak, G. In "Methods in Enzymology"; Colowick, S. P., Kaplan, N. O., Eds.; Academic Press: New York, 1969; Vol. 15, pp 392.

(12) Epoxy esters were obtained in 90% yield by treating a 0.5 M solution of **8** (or **14**) on CH_2Cl_2 with 2 equiv of *m*-chloroperbenzoic acid for 16 h. Excess peracid was destroyed with butadiene (0 °C). Washing (1.5 N NaOH, brine), drying ($NaSO_4$), filtration, and concentration gave material which on $LiAlH_4$ (or $LiAlD_4$) reduction yielded racemic **11** (or **17**) in 83% yield.

2.27 (bs, OH), 1.97 (bt, 1 H, J = 7 Hz), 1.77 (m, 1 H), 1.64 (m, 1 H), 1.24 and 1.23 (4:96, each s, total 3 H).

1-(+)-MTPA Esters of Racemic 3-Methylpentane-1,3,5-triol-2-*d* (12 and 13). Racemic epoxy alcohol **10** (3 mg), obtained by *m*-chloroperbenzoic acid (5 mg) epoxidation of **9** in 3 mL of CH_2Cl_2 at room temperature, was reduced with $LiAlH_4$ as described for **11**. Racemic **11** was then derivatized in the same manner as the preparation of **12** resulting in a diastereomeric mixture of **12** and **13**: MS, m/z 274 (10%), 189 (100%); IR ν 3400, 2170 (C–D), 1740, 1270 cm^{-1}; ^{1}H NMR δ 7.75–7.38 (m, 5 H), 4.49 (m, 2 H), 3.86 (m, 2 H), 3.54 (s, 3 H), 2.86 (bs, 0.5 H, OH), 2.84 (bs, 0.5 H, OH), 2.33 (bs, OH), 1.96 (m, 1 H), 1.76 (m, 1 H), 1.63 (m, 1 H), 1.24 and 1.23 (1:1, each s, total 3 H).

(2*R*,3*R*)-Mevalonic-2-*d* Acid Lactone (1). To a solution of **11** (2.11 g, 9 mmol) in 16 mL of H_2O and 4.1 mL of 15% NaOH, was added 2.25 g of $KMnO_4$ in four portions over a 30 min period at 0 °C. After all the oxidant was consumed (ca. 1 h), 2.1 mL of 15% NaOH was added and a 1.3-g portion of $KMnO_4$ was added. Usually, all starting material was consumed within 1 h (TLC) and excess oxidant was destroyed by addition of methanol (0.5 mL). Occasionally all of the second portion of $KMnO_4$ is consumed and a trace of starting material remains. More oxidant should not be added. The resultant mixture, which was kept in an ice bath during the course of reaction, was filtered through Celite and washed with 50 mL of H_2O and 50 mL of aqueous methanol (50%). The pH was adjusted to 2 with concentrated HCl. After 3 h 15% NaOH was added (pH 4) and the solution evaporated to dryness. The solid was triturated with acetone, and the salts were filtered off. The acetone solution was treated with 50 mg *p*-toluenesulfonic acid if TLC showed the presence of hydroxy acid (R_f 0.15; **1**, R_f 0.5; SiO_2, AcOEt). After addition of triethyl amine (0.1 mL) the solvent was evaporated and flash chromatography of the residue with AcOEt yielded pure **1** (1.12 g, 8.55 mmol, 85%) of $[\alpha]_D$ −19.2° (c 20): high-resolution MS, found M$^+$ m/z 131.0714, calcd for $C_6H_9D_1O_3$ m/z 131.0693; MS, m/z 132 (M$^+$ + 1, 9%), 116 (10%), 104 (22%), 71 (100%); IR ν 3420 (O–H), 2080 (C–D), 1730 cm^{-1} (C=O); ^{1}H NMR δ 4.56 (m, 1 H), 4.30 (m, 1 H), 2.44 (t, 1 H, J = 3 Hz), 1.87 (m, 2 H), 1.37 (s, 3 H).

(*Z*)-Ethyl 5-(2-Ethoxyethoxy)-3-methyl-2-pentenoate (14). Conversion of **7** (2.10 g, 9.81 mmol) to **14** followed the procedure for the conversion of **8**, except quenching with H_2O, gave **14** (1.97 g, 8.56 mmol, 87%): *Z*:*E* = 50:1; MS, m/z 200 (M$^+$ − C=O, 3.5%), 141 (100%), 113 (95%); IR ν 1715 (C=O), 1645 cm^{-1} (C=C); ^{1}H NMR δ 5.71 (bs, 1 H), 4.67 (q, 1 H, J = 7 Hz), 4.12 (q, 2 H, J = 7 Hz), 3.75–3.40 (m, 4 H), 2.87 (t, 2 H, J = 7 Hz), 2.13 (s, 0.06 H, *E* isomer), 1.93 (d, 2.94 H, J = 1.5 Hz), 1.27 (d, 3 H, J = 7 Hz), 1.25 (t, 3 H, J = 7 Hz), 1.17 (t, 3 H, J = 7 Hz).

(*Z*)-5-(2-Ethoxyethoxy)-3-methyl-2-penten-1-ol (15). Ester **14** (2.3 g, 10 mmol) was processed in the same way as **8** to give **15** (1.71 g, 9.1 mmol, 91%): MS, m/z 188 (M$^+$, 1.2%), 73 (100%); IR ν 3440 (O–H), 1660 (C=C), 1380, 1340, 1130 cm^{-1}; ^{1}H NMR δ 5.66 (bt, 1 H, J = 8 Hz), 4.66 (q, 1 H, J = 7 Hz), 3.98 (bd, 2 H, J = 7 Hz), 3.24–3.76 (m, 4 H), 2.34 (t, 2 H, J = 7 Hz), 1.74 (bs, 3 H), 1.28 (d, 3 H, J = 7 Hz), 1.16 (t, 3 H, J = 7 Hz).

(2*R*,3*R*)-5-(2-Ethoxyethoxy)-3-methylpentane-1,3-diol-2-*d* (17). Alcohol **15** (1.88 g, 10 mmol) was epoxidized in the same way as **9**. Reduction as described for **10** ($LiAlD_4$ instead of $LiAlH_4$) afforded pure **17** (1.68 g, 8.1 mmol, 81%): $[\alpha]_D$ −3.2° (c 20); MS, m/z 188 (M$^+$ − HOD, 6%), 162 (M$^+$ − OCH_2CH_3, 28%), 146 (23%), 115 (94%), 100 (55%), 73 (100%); IR ν 3400 (O–H), 2200 (C–D), 1380, 1130 cm^{-1}; ^{1}H NMR δ 4.68 (q, 1 H, J = 7 Hz), 3.95–3.40 (m, 6 H and OH), 3.27 (bs, O*H*), 1.90 (m, 1 H), 1.67 (m, 1 H), 1.64 (bs, 1 H), 1.30 (d, 3 H, J = 7 Hz), 1.27 (s, 3 H), 1.19 (t, 3 H, J = 7 Hz).

(2*S*,3*R*)-Mevalonic-2-*d* Acid Lactone (2). Following the procedure for **1**, **17** (1.98 g, 9.47 mmol) afforded pure **2** (1.07 g, 8.14 mmol, 86%), $[\alpha]_D$ −18.1° (c 20); high-resolution MS, found M$^+$ m/z 131.0704, calcd m/z 131.0693; MS, m/z 132 (M + 1$^+$, 3%), 131 (M$^+$, 2%), 116 (7%), 71 (100%); IR ν 3420 (O–H), 1720 cm^{-1} (C=O); ^{1}H NMR δ 4.56 (dt, 1 H, J = 6 and 13 Hz), 4.30 (dt, 1 H, J = 3.5 and 13 Hz), 3.35 (bs, O*H*), 2.60 (bs, 1 H), 1.87 (m, 2 H), 1.38 (s, 3 H).

(2*R*,3*S*)-5-(2-Ethoxyethoxy)-3-methylpentane-1,3-diol-2-*d* (19). Allylic alcohol **9** (1.88 g, 10 mmol) was converted to **19** (1.69 g, 8.2 mmol, 82%) in the same fashion as the preparation of **11** (unnatural (−)-diethyl tartrate was used in the epoxidation): $[\alpha]_D$ +2.9° (c 20); MS, m/z 162 (3%), 146 (20%), 115 (65%), 100 (85%), 73 (100%); IR ν 3400 (O–H), 2180 (C–D), 1380, 1130 cm^{-1}; ^{1}H NMR δ 4.68 (q, 1 H, J = 7 Hz), 3.20–3.95 (m, 6 H and 20 OH), 1.95 (m, 1 H), 1.78 (m, 1 H), 1.67 (m, 2 H), 1.30 (d, 3 H, J = 7 Hz), 1.27 (d, 3 H, J = 7 Hz), 1.19 (t, 3 H, J = 7 Hz).

(2*R*,3*S*)-1-Acetoxy-5-(2-ethoxyethoxy)-3-methylpentan-3-ol-2-*d* (20). A solution of **19** (1.25 g, 6 mmol) in 20 mL of dry CH_2Cl_2 containing 5 mL of triethyl amine, was treated with 3 mL of acetic anhydride. After stirring for 1 h, the reaction mixture was concentrated and flash chromatographed with hexane/AcOEt (4:1) to give pure **20** (1.47 g, 5.9 mmol, 98%): MS, m/z 204 (3%), 160 (70%), 73 (100%); IR ν 3510 (O–H), 2200, (C–D), 1740 (C=O), 1390, 1250, 1130 cm^{-1}; ^{1}H NMR δ 4.68 (q, 1 H, J = 7 Hz), 4.23 (d, 2 H, J = 7 Hz), 3.36–4.00 (m, 4 H), 3.27 (bs, OH), 2.05 (s, 3 H), 1.68–1.84 (m, 3 H), 1.32 (d, 3 H, J = 7 Hz), 1.25 (s, 3 H), 1.22 (t, 3 H, J = 7 Hz).

(3*S*,4*R*)-Mevalonic-4-*d* Acid Lactone (3). A solution of **20** (1.27 g, 5.1 mmol) in 20 mL methanol containing 50% aqueous acetic acid was stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo, and the residue taken up in 20 mL of acetone. Jones reagent (8 N, 3 mL) was added dropwise over 5 min with ice-bath cooling. After stirring for 30 min, excess oxidant was decomposed by the addition of methanol (0.5 mL). The supernant was decanted and the residue extracted with 50 mL of acetone. The combined acetone extract was filtered through Florosil and washed with methanol (50 mL). The filtrate was concentrated and treated with 2 mL of 1 *N* HCl in 5 mL of methanol for 2 h. The mixture was reconcentrated and treated with 50 mg of *p*-TsOH in 25 mL of acetone for 5 h. Flash column chromatography on the concentrated reaction mixture (after addition of 0.1 mL of triethyl amine) with AcOEt afforded pure **3** (495 mg, 3.78 mmol, 74%): $[\alpha]_D$ −18.4° (c 10); high-resolution MS, found M$^+$ m/z 131.0682, calcd m/z 131.0690; MS, m/z 131 (M$^+$, 8%), 104 (12%), 72 (100%); IR ν 3450 (O–H), 2190 (C–D), 1710 (C=O), 1240, 1130, 1050 cm^{-1}; ^{1}H NMR δ 4.50 (t, 1 H, J = 13 Hz), 4.30 (dd, 1 H, J = 4 and 13 Hz), 2.70 (d, 1 H, J = 18 Hz)8 2.46 (d, 1 H, J = 18 Hz), 1.97 (m, 1 H), 1.40 (s, 3 H).

(2*S*,3*R*)-5-(2-Ethoxyethoxy)-3-methylpentane-1,3-diol-2-*d* (22). Following the preparation procedure of **19** from **9** except that $LiAlD_4$ was used instead of $LiAlH_4$, **15** (1.88 g, 10.0 mmol) afforded **22** (1.71 g, 8.2 mmol, 82%): $[\alpha]_D$ +3.1° (MeOH, c 20); MS, m/z 188 (M$^+$ − HOD, 4%), 162 (26%), 146 (22%), 115 (90%), 100 (52%), 73 (100%); IR ν 3400 (O–H), 2200, 1380, 1130 cm^{-1}; ^{1}H NMR δ 4.66 (q, 1 H, J = 7 Hz), 3.30–4.00 (m, 6 H) 2.37 (bs, 1 H), 1.90 (m, 1 H), 1.66 (m, 1 H), 1.64 (bs, 1 H), 1.30 (d, 3 H, J = 7 Hz), 1.27 (d, 3 H, J = 7 Hz), 1.19 (t, 3 H, J = 7 Hz).

(2*S*,3*S*)-1-Acetoxy-5-(2-ethoxyethoxy)-3-methylpentan-3-ol-2-*d* The same procedure as for **20** was carried out with **22** to give **23** (765 mg, 3.45 mmol, 99%): MS, m/z 204 (20%), 188 (15%), 160 (40%), 115 (50%), 73 (100%); IR ν 3500 (O–H), 2190 (C–D), 1740 (C=O), 1390, 1240 cm^{-1}; ^{1}H NMR δ 4.69 (q, 1 H, J = 7 Hz), 4.23 (d, 2 H, J = 7 Hz), 3.38–3.96 (m, 4 H), 2.05 (m, 3 H), 1.30 (d, 3 H, J = 7 Hz), 1.24 (s, 3 H), 1.22 (t, 3 H, J = 7 Hz).

(3*S*,4*S*)-Mevalonic-4-*d* Acid Lactone (4). According to the procedure for the preparation of **3**, **23** (1.20 g, 4.8 mmol) was converted to the lactone **4** (500 mg, 3.8 mmol, 79%): $[\alpha]_D$ −16.6° (c 10, MeOH); high-resolution MS, found M$^+$ m/z 131.0700, calcd m/z 131.0693; MS, m/z 131 (M$^+$, 7%), 103 (10%), 72 (100%); IR ν 3500 (O–H), 2190 (C–D), 1710 (C=O), 1240 cm^{-1}; ^{1}H NMR δ 4.58 (dd, 1 H, J = 5 and 13 Hz), 4.30 (dd, 1 H, J = 3.5 and 13 Hz), 2.70 (dd, 1 H, J = 1.5 and 18 Hz), 2.46 (d, 1 H, J = 18 Hz), 1.86 (m, 1 H), 1.40 (s, 3 H).

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