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Synthesis of Deuterated Mevalonolactone Isotopomers

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A synthetic route was developed for the preparation of deuterated mevalonolactones. Using low-cost deuterated reagents, this route allows for the independent introduction of deuterium labeling into any carbon position or into any combination of positions. Following this approach, the synthesis of [6,6,6-$^2H_3$]mevalonolactone, [4,4,6,6,6-$^2H_5$]mevalonolactone, [5,5-$^2H_2$]mevalonolactone, [5,5,6,6,6-$^2H_5$]mevalonolactone, and [2,2,6,6,6-$^2H_5$]mevalonolactone is described.

Introduction

Modern methods for investigating biosynthetic pathways to natural products include genetic and enzymologic experiments, such as gene knockouts, expressions of genes or whole biosynthetic gene clusters in heterologous hosts, and incubations of purified enzymes with their natural substrates or analogs. Using isotopically labeled precursors, classical feeding experiments can give additional information and are in general easily carried out, as they are only limited by the availability of labeled compounds. The incorporation of the isotopic label into the natural product can be followed by the analysis of crude extracts, through a combination of chromatographic methods and mass spectrometry (mainly HPLC–MS or GC–MS) or by NMR spectroscopy completed after the purification of the natural product.[1] These facile approaches make feeding experiments a very powerful tool for the elucidation of biosynthetic pathways. A wide range of isotopically labeled compounds, including amino acids, sugars, C_2 and C_3 building blocks such as acetate and pyruvate, and other primary metabolites, are available from commercial suppliers. However, if more specialized questions are addressed, unusual precursors or precursors with an isotopic label in specific positions may be required, and therefore, synthesis may be necessary. These syntheses can be highly complex and laborious, and the isotopically labeled starting materials or reagents are usually expensive. Therefore, short, efficient, and flexible routes are required.

Besides radioactive isotopes such as ^{14}C and ^3H, most biosynthetic studies make use of ^{13}C or ^2H. Radioactive labels can be detected with very high sensitivity using radiographic methods. However, the health hazards and the high safety standards required for the manipulation of radioactive material are drawbacks. Feeding experiments with ^{13}C-labeled compounds can give insight into the origin of the carbon backbone of a natural product, and rearrangements of the carbon skeleton may also be followed. One of the most prominent examples is the discovery and elucidation of the deoxyxylulose phosphate pathway to plant and bacterial terpenoids, such as the ginkgolides from *Gingko biloba* and hopanoids from *Rhodopseudomonas palustris*.[2] In these studies, a labeling pattern in the terpenes was found which could not be explained by the well-known mevalonate pathway. In addition, a rearrangement in an early step of the newly discovered deoxyxylulose phosphate pathway was demonstrated. A major advantage of ^{13}C labeling is the convenient detection of its incorporation using ^{13}C NMR spectroscopy. As the natural abundance of ^{13}C is only about 1%, very low incorporation rates already result in a significant increase of the corresponding NMR signal. However, if the ^{13}C labeling occurs in different neighboring carbons and with high incorporation rates, highly complex ^{13}C NMR spectra may be obtained due to the ^{13}C-^{13}C couplings. Therefore, dilution experiments are sometimes performed to limit the percentage of recovered label in the natural product.[3]

The incorporation of deuterium can also be followed using NMR spectroscopy. As the natural abundance of ^1H is nearly 100%, higher incorporation rates are required for significant effects in the ^1H NMR spectrum. Deuterium labeling is particularly useful for investigating volatile natural products using GC–MS, because deuterated compounds have shorter retention times than their unlabeled analogs, and the incorporation of one deuterium usually results in a decrease of the retention index by one unit.[4] The shortened retention times are caused by an isotopic effect which results in a significantly shorter C–D bond compared to a C–H bond. This effect is not significant in the case of other isotopic pairs, such as a ^{13}C–H bond compared to a ^{12}C–H bond. As a consequence of the bond shortening, the polar-

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izability of a deuterated compound is lower than that for its unlabeled counterpart. Therefore, the van der Waals interactions between the deuterated material and the stationary phase of the GC are weaker, and this results in shorter retention times of the deuterated analyte. As a consequence, the mass spectra of the pure deuterated compounds are not superimposed by those of the unlabeled compounds.

For investigations of the biosynthesis of terpenoids, deuterated pathway intermediates are frequently required. The biosynthesis of terpenes proceeds from linear precursors, such as geranyl diphosphate (GPP, to monoterpenes), farnesyl diphosphate (FPP, to sesquiterpenes), or geranylgeranyl diphosphate (GGPP, to diterpenes), via cationic intermediates that are generated by abstraction of the diphosphate moiety or by protonation of an isoprenoid double bond.[5] The structurally complex polycyclic carbon backbone of a terpene is formed by cyclization steps in which olefinic double bonds attack cationic centers, and Wagner–Meerwein shifts and hydride migrations may occur. Termination mechanisms include deprotonating a late cationic intermediate or having it undergo a nucleophilic attack by water, for example. The hydride shifts and deprotonation steps can only be followed by using deuterated pathway intermediates, and few synthetic routes to deuterated isotopomers of mevalonolactone[6] or deoxyxylulose[7] have been published. Synthetic routes to isotopically labeled mevalonolactones and their applications in biosynthetic investigations have also been reviewed.[8] In a previous publication we reported the synthesis of [4,4,6,6,6-$^2H_5$]mevalonolactone (MVA), which was used to investigate the biosynthesis of geosmin to prove a critical hydride migration,[9] and of 2-methylisoborneol.[10] Both are frequently occurring volatiles produced by several streptomycetes and myxobacteria. Using the same synthetic strategy as that for [4,4,6,6,6-$^2H_5$]-MVA, the synthesis of further MVA isotopomers is reported herein.

Results and Discussion

The aim of our work was to develop a synthetic route to deuterated mevalonolactones that allows for the independent introduction of deuterium into any position or into any combination of different positions using low-cost deuterated reagents. Following this approach, compounds [6,6,6-$^2H_3$]MVA (**1a**), [4,4,6,6,6-$^2H_5$]MVA (**1b**), [5,5-$^2H_2$]-MVA (**1c**), [5,5,6,6,6-$^2H_5$]MVA (**1d**), and [2,2,6,6,6-$^2H_5$]-MVA (**1e**) were synthesized (Figure 1).

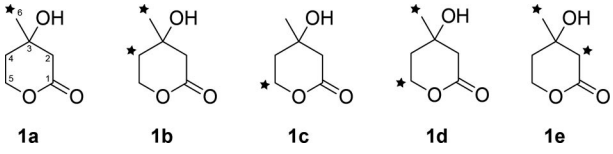
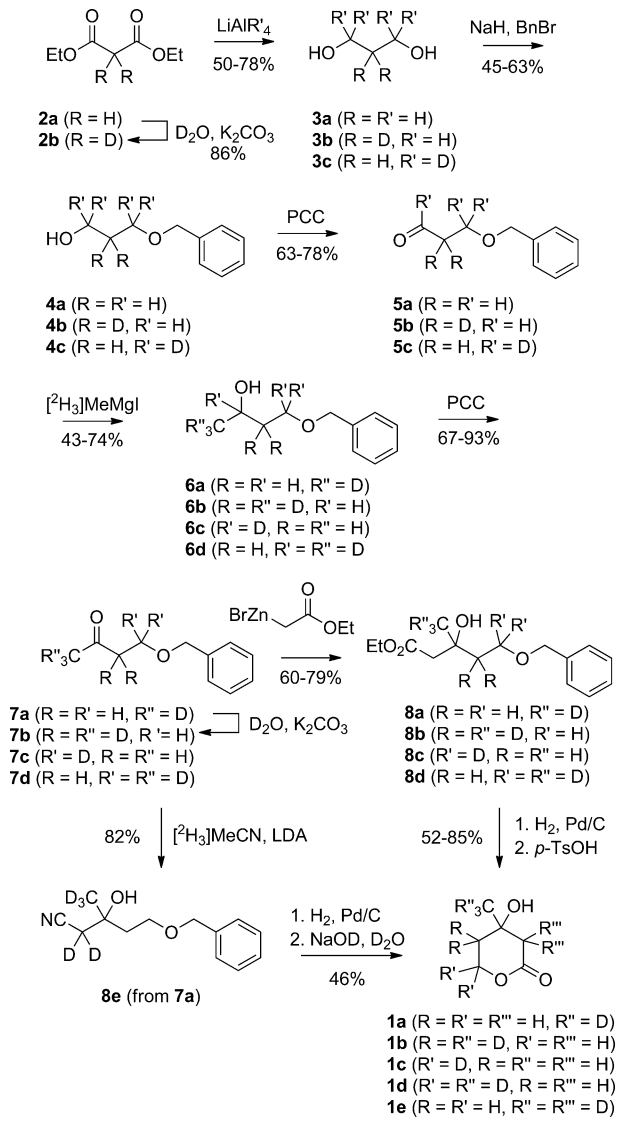


Figure 1. Synthesized deuterated mevalonolactones **1a**–**e**.

The original synthesis[9] of [4,4,6,6,6-$^2H_5$]MVA (**1b**) was carried out using propane-1,3-diol (**3a**, Scheme 1) as the starting material. Monoprotection of **3a** by treatment with NaH and benzyl bromide gave **4a** that was then oxidized using pyridinium chlorochromate (PCC) to the corresponding aldehyde **5a**. The first deuterium label was introduced by a Grignard reaction using [$^2H_3$]methylmagnesium iodide, prepared from [$^2H_3$]methyl iodide, and resulted in alcohol **6a**. Oxidation of **6a** with PCC afforded ketone **7a** which then underwent H/D exchange (hydrogen/deuterium exchange) with potassium carbonate in deuterium oxide to give **7b**. Subsequent addition of ethyl bromoacetate in a Reformatsky reaction with Rieke zinc yielded ester **8b**. Removal of the benzyl protecting group by a catalytic hydrogenation reaction resulted in the free alcohol without any detectable loss of the deuterium label according to ^1H NMR spectroscopy or GC–MS analysis. The product underwent a spontaneous partial cyclization which went to completion upon further treatment with *p*-TsOH to form [4,4,6,6,6-$^2H_5$]MVA (**1b**).



Scheme 1. Synthesis of deuterated mevalonolactones **1a**–**e**.

The same sequence of steps was carried out for the synthesis of [6,6,6-$^2H_3$]MVA (**1a**). In this case, the step introducing deuterium to **7a** to give **7b** was omitted, and **7a** was directly converted by the addition of ethyl bromoacetate into ester **8a**. For our generalized approach, this introduction of deuterium by H/D exchange with deuterium oxide was problematic, because the independent deuteration of either the methyl group or the methylene group next to the carbonyl function was not possible. A second problem with this reaction was described in a previous[9] publication, that is, the use of a relatively strong base such as sodium methoxide in MeOD for the H/D exchange resulted in the elimination of benzyl alcohol from **7a**, whereas the use of a mild base such as K_2CO_3 in deuterium oxide required a prolonged reaction time of seven days for the completion of the H/D exchange. To circumvent these problems, we developed a new synthetic route to [4,4,6,6,6-$^2H_5$]MVA (**1b**) starting from diethyl malonate (**2a**). The H/D exchange using potassium carbonate in deuterium oxide proceeded smoothly and gave **2b** with a deuterium content of >99% in the central methylene group. Lithium aluminium hydride reduction of **2b** gave **3b**, monobenzylation of the diol gave **4b**, and oxidation of the alcohol with PCC produced **5b** with a slight deuterium loss (<5%) caused by the acidity of the α-position. The Grignard reaction with [$^2H_3$]methylmagnesium iodide gave alcohol **6b**, and subsequent oxidation yielded ketone **7b** that was further processed to **1b** through the established route. Using the unlabeled Grignard reagent, methylmagnesium iodide, would allow for the synthesis of [4,4-$^2H_2$]MVA and, therefore, the independent introduction of deuterium into the 4- or 6-positions of mevalonolactone is possible with this route.

The synthesis of [5,5-$^2H_2$]MVA (**1c**) was carried out from **2a** by a reduction with lithium aluminium deuteride to give **3c**. The following steps included protection of **3c** to give benzyl ether **4c**, oxidation of the alcohol with PCC to give **5c**, and Grignard reaction of **5c** with methylmagnesium iodide to give **6c**. Oxidation of the alcohol to ketone **7c** was followed by the nucleophilic addition with ethyl bromoacetate to give **8c**. Removal of the benzyl protecting group followed by cyclization afforded **1c**. A drawback of this route was the loss of 50% of the deuterium label during the oxidation reactions to **5c** and **7c**. Similarly, [5,5,6,6,6-$^2H_5$]MVA (**1d**) was prepared from **5c** by treatment with [$^2H_3$]methylmagnesium iodide to yield **6d** that proceeded to the target compound through **7d** and **8d**.

Instead of the addition of ethyl bromoacetate through a Reformatsky reaction, the alternative nucleophilic addition of [$^2H_3$]acetonitrile to aldehyde **7a** was applied to the synthesis of [2,2,6,6,6-$^2H_5$]MVA (**1e**). The respective reaction gave compound **8e** that was deprotected by catalytic hydrogenation. Saponification of the nitrile was carried out with NaOD in deuterium oxide to prevent a deuterium washout in the methylene group adjacent to the nitrile function. This directly resulted in the formation of **1e**.

The major advantage of our synthetic method is the possibility of labeling any position of mevalonolactone. This can be accomplished by the H/D exchange of diethyl malonate with D_2O as in the synthesis of **1b**, by the reduction of diethyl malonate with $LiAlD_4$ as in the syntheses of **1c** and **1d**, by the Grignard reaction using [$^2H_3$]methylmagnesium iodide as in the syntheses of **1a**, **1b**, **1d**, and **1e**, or by the nucleophilic addition of [$^2H_3$]acetonitrile, instead of ethyl bromoacetate, to ketone **7c** as in the synthesis of **1e**. All these deuterated reagents are comparably cheap, and the introduction of deuterium at any carbon in mevalonolactone is possible. ^1H NMR spectroscopy and GC–MS analysis verified that all the deuterated isotopomers of mevalonolactone were obtained with a high percentage of deuterium content, usually more than 99% in the target positions. No deuterium was accidentally introduced at other carbons by potential side reactions. However, during the synthesis of aldehyde **5b** by oxidation with PCC, a slight loss of <5% of deuterium content was observed as a consequence of the C,H-acidity at the α-position. Fortunately, this loss will not be critical for the application of the mevalonolactone isotopomers derived from **5b** in biosynthetic investigations.

Conclusions

The known synthesis of [4,4,6,6,6-$^2H_5$]MVA (**1b**)[9] was improved and modified, resulting in a highly flexible route to deuterated mevalonolactones that may be independently labeled in any carbon position or in any combination of positions. The applicability of this route was demonstrated in the synthesis of four additional isotopomers of mevalonolactone, [6,6,6-$^2H_3$]MVA (**1a**), [5,5-$^2H_2$]MVA (**1c**), [5,5,6,6,6-$^2H_5$]MVA (**1d**), and [2,2,6,6,6-$^2H_5$]MVA (**1e**). Together with **1b**, these compounds are useful for investigating the biosynthesis of terpenoids. Our approach also makes new mevalonolactones available, as synthetic routes towards **1d** and **1e** were previously unpublished. Application of these labeled mevalonolactones to biosynthetic investigations will soon be carried out in our laboratory.

Experimental Section

General Synthetic Methods: Chemicals were purchased from Acros Organics (Geel, Belgium) or Sigma Aldrich Chemie GmbH (Steinheim, Germany) and used without further purification. Solvents were purified by distillation and dried according to standard methods. For all general procedures, the relative amounts of the reagents are given as equivalents (equiv.) referring to the molar ratios of the compounds, and the relative amounts of the solvents are given as the final concentrations of the transformed starting material (set to 1.0 equiv.). Thin-layer chromatography was performed with the 0.2 mm precoated plastic sheets Polygram® Sil G/UV$_{254}$ (Machery-Nagel). Column chromatography was carried out using Merck silica gel 60 (70–200 mesh). ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker AMX400 spectrometer, UV spectra were obtained with a Varian Cary 100 Bio, and IR spectra were recorded with a Bruker Tensor 27 ATR (attenuated total reflectance). GC–MS analyses were carried out with an Agilent 7890A connected to an Agilent 5975C inert mass detector fitted with a BPX-5 fused silica capillary column (25 m, 0.25 mm i. d., 0.25 μm film). Instrumental parameters were (1) inlet pressure, 77.1 kPa, He

23.3 mL min^{-1}, (2) injection volume, 2 μL, (3) transfer line, 300 °C, and (4) electron energy, 70 eV. The GC was programmed as follows: 5 min at 50 °C increasing at 5 °C min^{-1} to 320 °C, and operated in split mode (20:1, 60 s valve time). The carrier gas was He at 1 mL min^{-1}. Retention indices (*I*) were determined from a homologous series of *n*-alkanes (C_8–C_{38}).

[2,2-$^2H_2$]Diethyl Malonate (2b): To a solution of diethyl malonate (16.0 g, 100 mmol) in D_2O (200 mL) was added anhydrous K_2CO_3 (1.36 g, 10 mmol, 0.10 equiv.). The reaction mixture was stirred for 24 h at room temperature and afterwards extracted with diethyl ether (3×). The combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure to yield **2b** (14.0 g, 86.3 mmol, 86%) as a colorless liquid with a deuterium content of >99% as determined by ^{1}H NMR spectroscopy and GC–MS analysis. TLC (hexane/ethyl acetate, 10:1; R_f = 0.16). GC (BPX-5): *I* = 1078. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.21 (q, $^3J_{H,H}$ = 7.2 Hz, 4 H, 2 CH_2), 1.29 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6 (2 CO), 61.4 (2 CH_2), 41.2 (quint., $^1J_{C,D}$ = 20.2 Hz, CD_2), 14.0 (2 CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 192 (2) [M]$^+$, 135 (64), 117 (100), 90 (29), 62 (23), 44 (80). IR (ATR): $\tilde{\nu}$ = 2982 (w), 1729 (s), 1368 (w), 1247 (s), 1083 (s), 1021 (m) cm^{-1}.

General Procedure for the Preparation of Isotopomers of Propane-1,3-diol: As published by Lambert,[11] a 3 M solution of the respective isotopomer of diethyl malonate (**2a** or **2b**, 1.0 equiv.) in dry diethyl ether was added to a 1 M suspension of $LiAlH_4$ or $LiAlD_4$ (1.2 equiv.) in dry diethyl ether at 0 °C. The reaction mixture was heated to reflux for 8 h and stirred overnight at room temperature. A 1.2 M solution of NaOH (0.20 equiv.) in distilled water was added over a period of 4 h. The precipitate was filtered, and the residue was washed with diethyl ether and returned to the reaction flask. Tetrahydrofuran (THF) was added, and the mixture was heated to reflux for 30 min. Filtration was repeated, and the residue was washed again with diethyl ether. This procedure was repeated three times. The combined filtrates were evaporated to yield the pure diols as yellowish oils. The deuterium content was higher than 99% as determined by ^{1}H NMR spectroscopy and GC–MS analysis.

[2,2-$^2H_2$]Propane-1,3-diol (3b): Yield (5.25 g, 67.0 mmol, 78%), TLC (ethyl acetate, R_f = 0.11). GC [BPX-5, *N*-Methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA)]: *I* = 1050. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.85 (s, 4 H, 2 CH_2), 2.27 (s, 2 H, 2 OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.9 (2 CH_2), 33.3 (quint., $^1J_{C,D}$ = 19.2 Hz, CD_2) ppm. MS (EI, 70 eV, MSTFA): *m*/*z* (%) = 222 (<1) [M]$^+$, 207 (18), 177 (51), 147 (100), 132 (79), 117 (78), 103 (23), 73 (84), 59 (29), 45 (23). IR (ATR): $\tilde{\nu}$ = 3294 (br.), 2881 (w), 1033 (s), 784 (m) cm^{-1}.

[1,1,3,3-$^2H_4$]Propane-1,3-diol (3c): Yield (4.03 g, 50.4 mmol, 50%), TLC (ethyl acetate, R_f = 0.11). GC (BPX-5, MSTFA): *I* = 1045. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.18 (s, 2 H, 2 OH), 1.79 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.2 (quint., $^1J_{C,D}$ = 21.6 Hz, 2 CD_2), 33.6 (CH_2) ppm. MS (EI, 70 eV, MSTFA): *m*/*z* (%) = 224 (<1) [M]$^+$, 209 (10), 179 (25), 147 (100), 133 (50), 118 (32), 73 (47). IR (ATR): $\tilde{\nu}$ = 3301 (br.), 2922 (s), 2853 (s), 1457 (m), 1101 (s), 801 (s) cm^{-1}.

General Procedure for the Preparation of Isotopomers of 3-(Benzyloxy)-1-propanol: To a 1 M solution of sodium hydride (60% in mineral oil, 1.3 equiv.) in absolute dimethylformamide (DMF) was added the respective isotopomer of 1,3-propandiol (**3a**–**c**, 1.0 equiv.) at 0 °C. After stirring at 0 °C for 15 min, benzyl bromide (1.0 equiv.) was added at 0 °C. The reaction mixture was allowed to stir overnight at room temperature and then quenched with an aqueous solution of HCl (2 M). The mixture was extracted with diethyl ether, and the organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1:1) to give monoprotected alcohols **4a**–**c** as colorless oils. For **4b** and **4c**, a deuterium content of >99% determined by ^{1}H NMR spectroscopy and GC–MS analysis was found. For all three compounds the corresponding dibenzyl ethers were also formed in minor amounts (17–28%).

3-(Benzyloxy)-1-propanol (4a): Yield (10.6 g, 63.9 mmol, 63%), TLC (hexane/ethyl acetate, 1:1; R_f = 0.38). GC (BPX-5): *I* = 1437. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.25 (m, 5 H, 5 CH), 4.51 (s, 2 H, CH_2), 4.20 (br. s, 1 H), 3.77 (t, $^3J_{H,H}$ = 5.8 Hz, $^1J_{C,H}$ = 156.1 Hz, 2 H, CH_2), 3.64 (t, $^3J_{H,H}$ = 5.9 Hz, $^1J_{C,H}$ = 141.2 Hz, 2 H, CH_2), 1.85 (quint., $^3J_{H,H}$ = 5.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.2 (CH_2), 69.0 (CH_2), 61.5 (CH_2), 31.9 (CH_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 166 (2) [M]$^+$, 107 (62), 105 (10), 92 (16), 91 (100), 79 (26), 78 (8), 77 (24), 65 (28), 63 (8), 51 (13), 39 (13). IR (ATR): $\tilde{\nu}$ = 3402 (w), 3063 (w), 3031 (w), 2931 (w), 2863 (w), 1723 (m), 1495 (w), 1479 (w), 1453 (w), 1365 (w), 1178 (w), 1073 (s), 1025 (m), 912 (w), 736 (s), 697 (s), 610 (w). UV/Vis (CH_2Cl_2): λ_{max} (ε, L mol^{-1} cm^{-1}) = 258 (179), 253 (147), 227 (145) nm.

[2,2-$^2H_2$]-3-(Benzyloxy)-1-propanol (4b): Yield (5.28 g, 31.4 mmol, 47%), TLC (hexane/ethyl acetate, 2:1; R_f = 0.19). GC (BPX-5): *I* = 1435. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.37–7.25 (m, 5 H, 5 CH), 4.51 (s, 2 H, CH_2), 3.76 (s, 2 H, CH_2), 3.64 (s, 2 H, CH_2), 2.45 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.2 (CH_2), 69.1 (CH_2), 61.5 (CH_2), 31.4 (quint., $^1J_{C,D}$ = 19.4 Hz, CD_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 168 (4) [M]$^+$, 149 (6), 107 (90), 91 (100), 79 (33), 65 (27) 51 (12). IR (ATR): $\tilde{\nu}$ = 3383 (br.), 3031 (w), 2862 (w), 1092 (s), 1045 (s), 736 (s), 696 (s). UV/Vis (CH_2Cl_2): λ_{max} (ε, L mol^{-1} cm^{-1}) = 258 (162), 253 (133), 226 (79) nm.

[1,1,3,3-$^2H_4$]-3-(Benzyloxy)-1-propanol (4c): Yield (3.68 g, 21.6 mmol, 45%), TLC (hexane/ethyl acetate, 2:1; R_f = 0.15). GC (BPX-5): *I* = 1433. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.25 (m, 5 H, 5 CH), 4.51 (s, 2 H, CH_2), 2.50 (s, 1 H, OH), 1.82 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1 (Cq), 128.4 (2 CH), 127.6 (CH), 127.5 (2 CH), 73.1 (CH_2), 68.3 (quint., $^1J_{C,D}$ = 20.8 Hz, CD_2), 60.7 (quint., $^1J_{C,D}$ = 21.8 Hz, CD_2), 31.6 (CH_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 170 (4) [M]$^+$, 151 (5), 107 (81), 91 (100), 79 (34), 65 (29), 51 (16), 33 (43). IR (ATR): $\tilde{\nu}$ = 3382 (br.), 3064 (w), 2935 (w), 1453 (w), 1028 (m), 735 (s), 696 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, L mol^{-1} cm^{-1}) = 258 (225), 252 (218), 230 (637) nm.

General Procedure for the Preparation of Isotopomers of 3-(Benzyloxy)-1-propanal: To a 0.5 M solution of the respective isotopomer of 3-(benzyloxy)-1-propanol (**4a**–**c**, 1.0 equiv.) in absolute dichloromethane was added pyridinium chlorochromate (1.5 equiv.). After stirring at room temperature overnight, the reaction mixture was filtered through silica gel and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1) to give aldehydes **5a**–**c** as colorless liquids. A slight loss of deuterium content was observed for compound **5b** (<5%), whereas the deuterium content was higher than 99% for compound **5c** as determined by ^{1}H NMR spectroscopy and GC–MS analysis.

3-(Benzyloxy)-1-propanal (5a): Yield (8.17 g, 49.8 mmol, 78%), TLC (hexane/ethyl acetate, 3:1; R_f = 0.38). GC (BPX-5): *I* = 1387. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 9.78 (t, $^3J_{H,H}$ = 1.8 Hz, $^1J_{C,H}$ = 173.5 Hz, 1 H, CHO), 7.37–7.25 (m, 5 H, 5 CH), 4.52 (s, $^1J_{C,H}$ = 141.5 Hz, 2 H, CH_2), 3.80 (t, $^3J_{H,H}$ = 6.0 Hz, $^1J_{C,H}$ = 142.9 Hz, 2 H, CH_2), 2.68 (td, $^3J_{H,H}$ = 6.1 Hz, $^3J_{H,H}$ = 1.9 Hz,

$^1J_{C,H}$ = 126.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1 (CHO), 137.8 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.2 (CH_2), 63.8 (CH_2), 43.8 (CH_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 164 (<1) $[M]^+$, 120 (4), 107 (55), 92 (14), 91 (100), 89 (9), 79 (38), 78 (9), 77 (31), 65 (32), 63 (12), 51 (18), 50 (9), 39 (14). IR (ATR): $\tilde{\nu}$ = 3064 (w), 3031 (w), 2865 (w), 2733 (w), 1720 (s), 1496 (w), 1453 (w), 1394 (w), 1363 (w), 1203 (w), 1093 (s), 1027 (w), 909 (w), 886 (w), 737 (s), 697 (s), 606 (w) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, $L\,mol^{-1}\,cm^{-1}$) = 257 (214), 252 (121), 227 (179) nm.

[2,2-$^2H_2$]-3-(Benzyloxy)-1-propanal (5b): Yield (4.05 g, 24.4 mmol, 78%), TLC (hexane/ethyl acetate, 10:1, R_f = 0.13). GC (BPX-5): *I* = 1386. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 9.78 (s, 1 H, CHO), 7.36–7.26 (m, 5 H, 5 CH), 4.52 (s, 2 H, CH_2), 3.79 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2 (CHO), 137.8 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.2 (CH_2), 63.7 (CH_2), 43.3 (quint., $^1J_{C,D}$ = 14.1 Hz, CD_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 166 (<1) $[M]^+$, 120 (3), 107 (77), 91 (100), 79 (41), 65 (26), 51 (18). IR (ATR): $\tilde{\nu}$ = 3064 (w), 2862 (w), 1723 (s), 1094 (s), 1027 (m), 736 (s), 697 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, $L\,mol^{-1}\,cm^{-1}$) = 290 (24.6), 258 (201), 252 (170), 227 (123) nm.

[1,3,3-$^2H_3$]-3-(Benzyloxy)-1-propanal (5c): Yield (2.26 g, 14.0 mmol, 63%), TLC (hexane/ethyl acetate, 10:1; R_f = 0.13). GC (BPX-5): *I* = 1384. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.49–7.29 (m, 5 H, 5 CH), 4.52 (s, 2 H, CH_2), 2.66 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8 (t, $^1J_{C,D}$ = 26.3 Hz, CDO), 137.8 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.1 (CH_2), 63.0 (quint., $^1J_{C,D}$ = 21.9 Hz, CD_2), 43.4 (CH_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 167 (<1) $[M]^+$, 107 (73), 91 (100), 79 (36), 65 (30), 51 (19), 39 (13). IR (ATR): $\tilde{\nu}$ = 3064 (w), 2858 (w), 1711 (s), 1093 (s), 736 (s), 697 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, $L\,mol^{-1}\,cm^{-1}$) = 258 (188), 253 (152), 226 (83) nm.

General Procedure for the Preparation of Isotopomers of 4-(Benzyloxy)-2-butanol: To a 0.5 M solution of methylmagnesium iodide/[$^2H_3$]methylmagnesium iodide in absolute diethyl ether, prepared from methyl iodide/[$^2H_3$]methyl iodide (1.1 equiv.) and Mg (1.1 equiv.) was added a 2 M solution of the respective isotopomer of 3-(benzyloxy)-1-propanal (**5a**–**c**, 1.0 equiv.) in absolute diethyl ether at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was quenched with a saturated solution of NH_4Cl and then extracted with Et_2O. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1) to give alcohols **6a**–**d** as colorless liquids. No loss of deuterium content was observed by ^1H NMR spectroscopy or GC–MS analysis.

[1,1,1-$^2H_3$]-4-(Benzyloxy)-2-butanol (6a): Yield (4.42 g, 24.2 mmol, 70%) TLC (hexane/ethyl acetate, 3:1; R_f = 0.21). GC (BPX-5): *I* = 1462. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.25 (m, 5 H, 5 CH), 4.52 (s, $^1J_{C,H}$ = 141.7 Hz, 2 H, CH_2), 3.99 (dd, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 2.7 Hz, 1 H, CH), 3.70 (ddd, $^3J_{H,H}$ = 9.4 Hz, $^3J_{H,H}$ = 5.6 Hz, $^3J_{H,H}$ = 4.9 Hz, 1 H, CH_2), 3.63 (ddd, $^3J_{H,H}$ = 9.4 Hz, $^3J_{H,H}$ = 7.9 Hz, $^3J_{H,H}$ = 4.7 Hz, 1 H, CH_2), 2.90 (br. s, 1 H, OH), 1.81–1.67 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.2 (CH_2), 69.1 (CH_2), 67.3 (CH), 38.1 (CH_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 183 (<1) $[M]^+$, 161 (11), 120 (11), 108 (9), 107 (30), 105 (12), 92 (14), 91 (100), 89 (8), 79 (21), 78 (9), 77 (23), 65 (29), 63 (8), 59 (9), 51 (13), 48 (36), 46 (17), 43 (9), 39 (10). IR (ATR): $\tilde{\nu}$ = 3409 (w), 3064 (w), 3031 (w), 2915 (w), 2862 (w), 2222 (w), 1453 (w), 1363 (w), 1206 (w), 1089 (s), 1028 (m), 909 (w), 736 (s), 697 (s), 610 (m), 553 (w) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, $L\,mol^{-1}\,cm^{-1}$) = 258 (202), 252 (174), 226 (125) nm.

[1,1,1,3,3-$^2H_5$]-4-(Benzyloxy)-2-butanol (6b): Yield (2.99 g, 16.2 mmol, 54%), TLC (hexane/ethyl acetate, 3:1; R_f = 0.18). GC (BPX-5): *I* = 1458. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.37–7.25 (m, 5 H, 5 CH), 4.52 (s, 2 H, CH_2), 3.98 (s, 1 H, CH), 3.69 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, CH_2), 3.62 (d, $^3J_{H,H}$ = 9.4 Hz, 1 H, CH_2), 2.82 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.3 (CH_2), 68.9 (CH_2), 67.2 (CH), 37.5 (quint., $^1J_{C,D}$ = 19.0 Hz, CD_2), 22.4 (sept., $^1J_{C,D}$ = 18.9 Hz, CD_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 185 (<1) $[M]^+$, 166 (23), 120 (25), 107 (51), 91 (100), 79 (24), 65 (28), 48 (26). IR (ATR): $\tilde{\nu}$ = 3413 (br.), 3064 (w), 2931 (w), 1072 (s), 1043 (s), 734 (s), 696 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, $L\,mol^{-1}\,cm^{-1}$) = 228 (53) nm.

[2,4,4-$^2H_3$]-4-(Benzyloxy)-2-butanol (6c): Yield (1.95 g, 10.7 mmol, 74%), TLC (hexane/ethyl acetate, 3:1; R_f = 0.23). GC (BPX-5): *I* = 1460. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.25 (m, 5 H, 5 CH), 4.49 (s, $^1J_{C,H}$ = 141.7 Hz, 2 H, CH_2), 2.88 (br. s, 1 H, OH), 1.76–1.67 (m, 2 H, CH_2), 1.18 (s, $^1J_{C,H}$ = 125.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6 (Cq), 128.1 (2 CH), 127.4 (CH), 127.3 (2 CH), 72.8 (CH_2), 37.4 (CH_2), 22.9 (CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 183 (<1) $[M]^+$, 164 (18), 150 (2), 122 (14), 107 (35), 91 (100), 77 (27), 65 (23), 51 (18), 42 (6). IR (ATR): $\tilde{\nu}$ = 3413 (br.), 3064 (w), 2966 (w), 2082 (w), 1453 (w), 1144 (s), 941 (m), 696 (s) cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε, $L\,mol^{-1}\,cm^{-1}$) = 258 (197), 253 (161), 235 (117) nm.

[1,1,1,2,4,4-$^2H_6$]-4-(Benzyloxy)-2-butanol (6d): Yield (1.12 g, 6.02 mmol, 43%), TLC (hexane/ethyl acetate, 3:1; R_f = 0.18). GC (BPX-5): *I* = 1456. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.37–7.25 (m, 5 H, 5 CH), 4.52 (s, 2 H, CH_2), 2.87 (s, 1 H, OH), 1.72 (dd, $^2J_{H,H}$ = 25.3 Hz, $^4J_{H,H}$ = 14.6 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.2 (CH_2), 68.2 (quint., $^1J_{C,D}$ = 21.9 Hz, CD_2), 66.8 (t, $^1J_{C,D}$ = 22.1 Hz, CD), 37.7 (CH_2), 22.1 (sept., $^1J_{C,D}$ = 19.2 Hz, CD_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 186 (<1) $[M]^+$, 167 (12), 122 (12), 107 (28), 91 (100), 77 (29), 65 (30), 49 (51). IR (ATR): $\tilde{\nu}$ = 3396 (br.), 3064 (w), 2932 (w), 1172 (m), 1101 (s), 736 (s), 696 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, $L\,mol^{-1}\,cm^{-1}$) = 257 (239), 252 (244), 230 (591) nm.

General Procedure for the Preparation of Isotopomers of 4-(Benzyloxy)-2-butanone: To a 0.2 M solution of the respective isotopomer of 4-(benzyloxy)-2-butanol (**6a**–**d**, 1.0 equiv.) in absolute dichloromethane was added pyridinium chlorochromate (1.5 equiv.). After stirring at room temperature for 4 h, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 5:1) to give methyl ketones **7a**–**d** as colorless liquids. No loss of deuterium content was observed by ^1H NMR spectroscopy or GC–MS analysis.

[1,1,1-$^2H_3$]-4-(Benzyloxy)-2-butanone (7a): Yield (3.82 g, 21.1 mmol, 93%), TLC (R_f = 0.21). GC (BPX-5): *I* = 1463. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.25 (m, 5 H, 5 CH), 4.50 (s, $^1J_{C,H}$ = 141.4 Hz, 2 H, CH_2), 3.73 (t, $^3J_{H,H}$ = 6.3 Hz, $^1J_{C,H}$ = 143.3 Hz, 2 H, CH_2), 2.70 (t, $^3J_{H,H}$ = 6.3 Hz, $^1J_{C,H}$ = 126.0 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.2 (CO), 138.0 (Cq), 128.3 (2 CH), 127.6 (3 CH), 73.2 (CH_2), 65.2 (CH_2), 43.7 (CH_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 181 (<1) $[M]^+$, 120 (12), 107 (35), 92 (11), 91 (82), 89 (8), 79 (20), 78 (9), 77 (25), 75 (11), 65 (29), 63 (9), 57 (8), 51 (15), 46 (100), 39 (12). IR (ATR): $\tilde{\nu}$ = 3064 (w), 3031 (w), 2866 (w), 1708 (s), 1496 (w), 1453 (w), 1365 (m), 1250 (w), 1179 (m), 1100 (s), 1074 (s), 1026 (m), 737 (s), 698 (s), 610 (w), 543 (w) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, $L\,mol^{-1}\,cm^{-1}$) = 258 (195), 253 (161), 227 (171) nm.

[1,1,1,3,3-$^2H_5$]-4-(Benzyloxy)-2-butanone (7b): Yield (2.30 g, 12.6 mmol, 78%), TLC (hexane/ethyl acetate, 5:1; R_f = 0.24). GC (BPX-5): I = 1458. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.26 (m, 5 H, 5 CH), 4.51 (s, 2 H, CH_2), 3.72 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5 (CO), 138.0 (Cq), 128.4 (2 CH), 127.64 (2 CH), 127.62 (CH), 73.2 (CH_2), 65.1 (CH_2), 43.1 (quint., $^1J_{C,D}$ = 19.2 Hz, CD_2), 29.7 (sept., $^1J_{C,D}$ = 19.4 Hz, CD_3) ppm. MS (EI, 70 eV): m/z (%) = 183 (<1) $[M]^+$, 120 (18), 107 (86), 91 (100), 77 (56), 65 (49), 46 (99). IR (ATR): $\tilde{\nu}$ = 3064 (w), 2865 (w), 1706 (s), 1207 (m), 1094 (s), 737 (s), 689 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, L mol^{-1} cm^{-1}) = 258 (215), 252 (199), 227 (137) nm.

[4,4-$^2H_2$]-4-(Benzyloxy)-2-butanone (7c): Yield (1.40 g, 7.74 mmol, 74%) TLC (hexane/ethyl acetate, 3:1; R_f = 0.34). GC (BPX-5): I = 1463. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.35–7.25 (m, 5 H, 5 CH), 4.50 (s, $^1J_{C,H}$ = 141.6 Hz, 2 H, CH_2), 2.69 (s, $^1J_{C,H}$ = 125.0 Hz, 2 H, CH_2), 2.17 (s, $^1J_{C,H}$ = 127.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.1 (CO), 138.0 (Cq), 128.3 (2 CH), 127.63 (2 CH), 127.61 (CH), 73.1 (CH_2), 43.5 (CH_2), 30.4 (CH_3) ppm. MS (EI, 70 eV): m/z (%) = 180 (<1) $[M]^+$, 122 (12), 107 (65), 91 (100), 79 (34), 65 (29), 51 (18), 43 (84). IR (ATR): 3064 (w), 2856 (w), 1714 (s), 1361 (m), 1102 (s), 698 (s) cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε, L mol^{-1} cm^{-1}) = 258 (207), 253 (170), 233 (121) nm.

[1,1,1,4,4-$^2H_5$]-4-(Benzyloxy)-2-butanone (7d): Yield (739 mg, 4.04 mmol, 67%), TLC (hexane/ethyl acetate, 5:1; R_f = 0.24). GC (BPX-5): I = 1458. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.25 (m, 5 H, 5 CH), 4.51 (s, 2 H, CH_2), 2.70 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.3 (CO), 138.0 (Cq), 128.3 (2 CH), 127.6 (2 CH), 127.6 (CH), 64.5 (quint., $^1J_{C,D}$ = 21.8 Hz, CD_2), 43.5 (CH_2), 29.7 (sept., $^1J_{C,D}$ = 19.4 Hz, CD_3) ppm. MS (EI, 70 eV): m/z (%) = 183 (8) $[M]^+$, 165 (2), 122 (36), 107 (100), 91 (92), 77 (18). IR (ATR): $\tilde{\nu}$ = 3064 (w), 2858 (w), 1708 (s), 1164 (m), 1099 (s), 737 (s), 698 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, L mol^{-1} cm^{-1}) = 258 (204), 252 (174), 227 (151) nm.

General Procedure for the Preparation of Isotopomers of Ethyl 5-(Benzyloxy)-3-hydroxy-3-methylpentanoate: To a 2 M solution of naphthalene (3 equiv.) in absolute THF was added lithium (3 equiv.). After consumption of the lithium, a 1 M suspension of $ZnCl_2$ (1.5 equiv.) in absolute THF was added dropwise to the green solution. Stirring was continued for 30 min, and then a 2 M solution of the respective isotopomer of 4-(benzyloxy)-2-butanone (**7a–d**, 1.0 equiv.) in absolute THF and ethyl bromoacetate (1.3 equiv.) was added dropwise. The reaction was stirred at room temperature for 3 h and quenched with a saturated solution of aqueous NH_4Cl. After extracting with diethyl ether, the organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 4:1) to give esters **8a–d** as colorless liquids. No loss of deuterium content was observed by ^{1}H NMR spectroscopy or GC–MS analysis.

Ethyl [6,6,6-$^2H_3$]-5-(Benzyloxy)-3-hydroxy-3-methylpentanoate (8a): Yield (1.42 g, 5.28 mmol, 70%), TLC (hexane/ethyl acetate, 4:1; R_f = 0.20). GC (BPX-5): I = 1918. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.25 (m, 5 H, 5 CH), 4.50 (s, 2 H, CH_2), 4.15 (dq, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH_2), 4.12 (dq, $^2J_{H,H}$ = 10.9 Hz, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH_2), 3.95 (br. s, 1 H), 3.69 (dt, $^2J_{H,H}$ = 9.8 Hz, $^3J_{H,H}$ = 6.1 Hz, 1 H, CH_2), 3.66 (dt, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 6.2 Hz, 1 H, CH_2), 2.57 (d, $^2J_{H,H}$ = 15.3 Hz, $^1J_{C,H}$ = 129.4 Hz, 1 H, CH_2), 2.50 (d, $^2J_{H,H}$ = 15.3 Hz, $^1J_{C,H}$ = 128.6 Hz, 1 H, CH_2), 1.93 (dt, $^2J_{H,H}$ = 14.4 Hz, $^3J_{H,H}$ = 6.1 Hz, 1 H, CH_2), 1.88 (dt, $^2J_{H,H}$ = 14.5 Hz, $^3J_{H,H}$ = 6.3 Hz, 1 H, CH_2), 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, $^1J_{C,H}$ = 127.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (CO), 137.9 (Cq), 128.3 (2 CH), 127.6 (3 CH), 73.2 (CH_2), 70.6 (Cq), 66.7 (CH_2), 60.4 (CH_2), 45.4 (CH_2), 40.3 (CH_2), 14.1 (CH_3) ppm. MS (EI, 70 eV): m/z (%) = 269 (<1) $[M]^+$, 163 (17), 145 (11), 134 (8), 92 (11), 91 (100), 88 (12), 79 (11), 77 (12), 72 (8), 65 (16), 46 (23). IR (ATR): $\tilde{\nu}$ = 3498 (w), 3064 (w), 3031 (w), 2981 (w), 2936 (w), 2867 (w), 2229 (w), 1728 (s), 1454 (w), 1369 (m), 1333 (w), 1193 (s), 1096 (s), 1026 (s), 907 (w), 850 (w), 736 (s), 698 (s), 598 (w) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, L mol^{-1} cm^{-1}) = 258 (243), 252 (220), 227 (298) nm.

Ethyl [4,4,6,6,6-$^2H_5$]-5-(Benzyloxy)-3-hydroxy-3-methylpentanoate (8b): Yield (2.69 g, 9.93 mmol, 79%), TLC (hexane/ethyl acetate, 4:1; R_f = 0.20). GC (BPX-5): I = 1915. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.37–7.25 (m, 5 H, 5 CH), 4.49 (s, 2 H, CH_2), 4.15 (dq, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH_2), 4.12 (dq, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH_2), 3.95 (br. s, 1 H, OH), 3.67 (s, 2 H, CH_2), 2.57 (d, $^2J_{H,H}$ = 15.2 Hz, 1 H, CH_2), 2.49 (d, $^2J_{H,H}$ = 15.3 Hz, 1 H, CH_2), 1.24 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (CO), 137.6 (Cq), 128.0 (2 CH), 127.32 (CH), 127.31 (2 CH), 72.9 (CH_2), 70.2 (Cq), 66.5 (CH_2), 60.1 (CH_2), 45.1 (CH_2), 13.8 (CH_3) ppm. MS (EI, 70 eV): m/z (%) = 253 (<1) $[M - H_2O]^+$, 184 (1), 165 (21), 147 (12), 134 (8), 115 (5), 107 (6), 91 (100), 74 (10), 65 (11), 46 (19).

Ethyl [5,5-$^2H_2$]-5-(Benzyloxy)-3-hydroxy-3-methylpentanoate (8c): Yield (528 mg, 1.97 mmol, 60%), TLC (hexane/ethyl acetate, 4:1; R_f = 0.14). GC (BPX-5): I = 1921. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.26 (m, 5 H, 5 CH), 4.50 (s, 2 H, CH_2), 4.15 (dq, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH_2), 4.12 (dq, $^2J_{H,H}$ = 10.9 Hz, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH_2), 3.97 (br. s, 1 H, OH), 2.57 (d, $^2J_{H,H}$ = 15.2 Hz, $^1J_{C,H}$ = 129.3 Hz, 1 H, CH_2), 2.49 (d, $^2J_{H,H}$ = 15.2 Hz, $^1J_{C,H}$ = 128.4 Hz, 1 H, CH_2), 1.92 (d, $^2J_{H,H}$ = 14.9 Hz, 1 H, CH_2), 1.87 (d, $^2J_{H,H}$ = 14.8 Hz, 1 H, CH_2), 1.28 (s, $^1J_{C,H}$ = 127.0 Hz, 3 H, CH_3), 1.25 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (CO), 138.0 (Cq), 128.4 (2 CH), 127.7 (CH), 127.6 (2 CH), 73.1 (CH_2), 70.7 (Cq), 65.2 (Cq), 60.6 (CH_2), 45.5 (CH_2), 40.1 (CH_2), 27.1 (CH_3), 14.1 (CH_3) ppm. MS (EI, 70 eV): m/z (%) = 268 (<1) $[M]^+$, 181 (3), 142 (46), 144 (24), 131 (18), 107 (17), 91 (100), 77 (28), 65 (34), 43 (63). IR (ATR): $\tilde{\nu}$ = 3497 (br.), 2978 (w), 2080 (w), 1727 (s), 1372 (m), 1193 (s), 698 (s). UV/Vis ($CHCl_3$): λ_{max} (ε, L mol^{-1} cm^{-1}) = 258 (285), 252 (260), 239 (234) nm.

Ethyl [5,5,6,6,6-$^2H_5$]-5-(Benzyloxy)-3-hydroxy-3-methylpentanoate (8d): Yield (540 mg, 1.85 mmol, 62%), TLC (hexane/ethyl acetate, 5:1; R_f = 0.15). GC (BPX-5): I = 1917. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.36–7.26 (m, 5 H, 5 CH), 4.50 (s, 2 H, CH_2), 4.15 (dq, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH_2), 4.11 (dq, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.0 Hz, 1 H, CH_2), 2.57 (d, $^2J_{H,H}$ = 15.3 Hz, 1 H, CH_2), 2.49 (d, $^2J_{H,H}$ = 15.2 Hz, 1 H, CH_2), 1.92 (d, $^2J_{H,H}$ = 14.8 Hz, 1 H, CH_2), 1.87 (d, $^2J_{H,H}$ = 14.8 Hz, 1 H, CH_2), 1.25 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (CO), 138.3 (Cq), 128.7 (2 CH), 127.9 (CH), 127.9 (2 CH), 73.4 (CH_2), 70.9 (Cq), 66.4 (quint., $^1J_{C,D}$ = 21.6 Hz, CD_2), 60.7 (CH_2), 45.8 (CH_2), 40.4 (CH_2), 14.4 (CH_3) ppm. MS (EI, 70 eV): m/z (%) = 271 (<1) $[M]^+$, 165 (19), 147 (12), 134 (6), 107 (6), 91 (100), 77 (11), 65 (13). IR (ATR): $\tilde{\nu}$ = 3493 (br.), 3064 (w), 2938 (w), 1728 (s), 1195 (s), 1026 (s), 736 (s), 697 (s) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, L mol^{-1} cm^{-1}) = 257 (285), 252 (296), 228 (433) nm.

General Procedure for the Preparation of Isotopomers of Mevalonolactone: A 0.1 M solution of the respective isotopomer of 5-(benzyloxy)-3-hydroxy-3-methylpentanoate (**8a–d**, 1.0 equiv.) was dissolved in diethyl ether and a catalytic amount of Pd/C (10 wt.%

Pd, 0.05 equiv.) was added. The mixture was stirred in a high pressure reactor (HR-100, Berghof, Eningen) under a hydrogen atmosphere (35 bar) at 40 °C until all of the starting material was consumed (90 min). The mixture was filtered through silica gel to give the deprotected alcohols as colorless oils. This crude material was dissolved in dichloromethane to give a 0.1 M solution, and *p*-toluenesulfonic acid (0.10 equiv.) was added. The mixture was stirred overnight and concentrated in vacuo. Column chromatography on silica gel (diethyl ether) gave the mevalonolactones **1a**–**d** as colorless oils. No loss of deuterium content was observed by ^{1}H NMR spectroscopy or GC–MS analysis.

[6,6,6-$^2H_3$]Mevalonolactone (1a): Yield (378 mg, 2.84 mmol, 59%), TLC (diethyl ether, R_f = 0.15). GC (BPX-5, MSTFA): I = 1388. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.62 (ddd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 6.8 Hz, 1 H, CH_2), 4.35 (ddd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 4.7 Hz, $^3J_{H,H}$ = 4.4 Hz, 1 H, CH_2), 3.05 (br. s, 1 H, OH), 2.66 (dt, $^2J_{H,H}$ = 17.4 Hz, $^4J_{H,H}$ = 1.3 Hz, 1 H, CH_2), 2.50 (d, $^2J_{H,H}$ = 17.4 Hz, 1 H, CH_2), 1.93–1.91 (m, 1 H, CH_2), 1.90 (dd, $^3J_{H,H}$ = 4.6 Hz, $^4J_{H,H}$ = 1.3 Hz, 1 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (CO), 67.7 (Cq), 66.2 (CH_2), 44.4 (CH_2), 35.5 (CH_2), 28.6 (sept., $^1J_{C,D}$ = 19.3 Hz, CD_3) ppm. MS (EI, 70 eV, MSTFA): m/z (%) = 205 (<1) $[M]^+$, 190 (9), 149 (13), 148 (100), 147 (29), 119 (10), 118 (2), 117 (12), 101 (12), 76 (28), 75 (44), 74 (10), 73 (50), 61 (9), 59 (14), 58 (14), 47 (13), 46 (28), 45 (35), 44 (15), 43 (25), 42 (32), 41 (12). IR (ATR): $\tilde{\nu}$ = 3420 (w), 2974 (w), 2922 (w), 2227 (w), 1716 (s), 1474 (w), 1399 (m), 1305 (w), 1263 (s), 1228 (s), 1172 (m), 1140 (w), 1108 (s), 1071 (s), 1021 (w), 998 (s), 976 (m), 931 (w), 883 (w), 821 (m), 787 (w), 731 (m), 652 (m), 575 (m) cm^{-1}. The ^{1}H and ^{13}C NMR spectroscopic data closely resembled those reported previously.[6c]

[4,4,6,6,6-$^2H_5$]Mevalonolactone (1b): Yield (1.14 g, 8.44 mmol, 85%) TLC (ethyl acetate, R_f = 0.10). GC (BPX-5, MSTFA): I = 1385. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.60 (d, $^2J_{H,H}$ = 11.3 Hz, 1 H, CH_2), 4.34 (d, $^2J_{H,H}$ = 11.3 Hz, 1 H, CH_2), 2.71 (br. s, 1 H, OH), 2.66 (d, $^2J_{H,H}$ = 17.4 Hz, 1 H, CH_2), 2.52 (d, $^2J_{H,H}$ = 17.3 Hz, 1 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (CO), 68.0 (Cq), 65.9 (CH_2), 44.6 (CH_2) ppm. MS (EI, 70 eV, MSTFA): m/z (%) = 207 (<1) $[M]^+$, 192 (12), 162 (11), 150 (100), 133 (5), 118 (44), 103 (11), 73 (39), 59 (6), 46 (15). IR (ATR): $\tilde{\nu}$ = 3417 (br.), 2974 (w), 2917 (w), 1704 (s), 1398 (m), 1240 (s), 1041 (s), 859 (m) cm^{-1}. The ^{1}H and ^{13}C NMR spectroscopic data closely matched those reported previously.[9]

[5,5-$^2H_2$]Mevalonolactone (1c): Yield (169 mg, 1.28 mmol, 70%), TLC (ethyl acetate, R_f = 0.13). GC (BPX-5, MSTFA): I = 1387. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.71 (br. s, 1 H, OH), 2.66 (ddd, $^2J_{H,H}$ = 17.4 Hz, $^4J_{H,H}$ = 1.7 Hz, $^4J_{H,H}$ = 1.2 Hz, $^1J_{C,H}$ = 133.0 Hz, 1 H, CH_2), 2.51 (d, $^2J_{H,H}$ = 17.4 Hz, $^2J_{C,H}$ = –6.9 Hz, 1 H, CH_2), 1.92 (d, $^2J_{H,H}$ = 14.7 Hz, $^1J_{C,H}$ = 128.6 Hz, 1 H, CH_2), 1.88 (d, $^2J_{H,H}$ = 14.7 Hz, $^1J_{C,H}$ = 128.6 Hz, 1 H, CH_2), 1.39 (s, $^1J_{C,H}$ = 126.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (CO), 68.0 (Cq), 65.5 (quint., $^1J_{C,D}$ = 23.2 Hz, CD_2), 44.6 (CH_2), 35.6 (CH_2), 29.7 (CH_3) ppm. MS (EI, 70 eV, MSTFA): m/z (%) = 204 (<1) $[M]^+$, 189 (13), 157 (5), 147 (100), 115 (77), 75 (54), 59 (13), 43 (36). IR (ATR): $\tilde{\nu}$ = 3418 (br.), 2969 (w), 1704 (s), 1260 (s), 1120 (s), 1024 (s), 861 (m) cm^{-1}.

[5,5,6,6,6-$^2H_5$]Mevalonolactone (1d): Yield (130 mg, 0.96 mmol, 52%) TLC (diethyl ether, R_f = 0.10). GC (BPX-5, MSTFA): I = 1385. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.98 (s, 1 H, OH), 2.66 (dt, $^2J_{H,H}$ = 17.5 Hz, $^4J_{H,H}$ = 1.4 Hz, 1 H, CH_2), 2.50 (d, $^2J_{H,H}$ = 17.4 Hz, 1 H, CH_2), 1.90 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (CO), 67.7 (Cq), 65.6 (quint., $^1J_{C,D}$ = 22.9 Hz, CD_2), 44.5 (CH_2), 35.4 (CH_2), 28.6 (sept., $^1J_{C,D}$ = 19.5 Hz, CD_3) ppm. MS (EI, 70 eV, MSTFA): m/z (%) = 207 (<1) $[M]^+$, 192 (13), 160 (6), 150 (100), 118 (65), 102 (7), 73 (30) 45 (16). IR (ATR): $\tilde{\nu}$ = 3418 (br.), 1704 (s), 1292 (s) 1156 (m), 1102 (s), 871 (m) cm^{-1}.

[2,2,6,6,6-$^2H_5$]-5-(Benzyloxy)-3-hydroxy-3-methylpentanenitrile (8e): To a solution of diisopropylamine (2.70 g, 26.7 mmol, 1.1 equiv.) in anhydrous THF (25 mL) under nitrogen was added dropwise *n*BuLi (1.6 M in hexane, 16.7 mL, 26.7 mmol, 1.1 equiv.) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was cooled to –90 °C. A solution of [$^2H_3$]acetonitrile (1.07 g, 24.3 mmol, 1.0 equiv.) in anhydrous THF (15 mL) was added followed by addition of the ketone (**7a**, 4.44 g, 24.3 mmol, 1.0 equiv.). The reaction mixture was stirred at –90 °C for 1 h and then warmed to room temperature overnight. The mixture was hydrolyzed by the addition of an aqueous saturated solution of NH_4Cl. The aqueous layer was extracted with diethyl ether (3×), the organic phase was dried with $MgSO_4$, and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (5:1) to give **8e** (4.45 g, 19.9 mmol, 82%) as a pale yellow liquid and with a deuterium content of >99% determined by ^{1}H NMR spectroscopy and GC–MS analysis. TLC (hexane/ethyl acetate, 1:1; R_f = 0.45). GC (BPX-5): I = 1822. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.38–7.27 (m, 5 H, 5 CH), 4.52 (s, $^1J_{C,H}$ = 142.2 Hz, 2 H, CH_2), 3.87 (br. s, 1 H, OH), 3.79–3.69 (m, 2 H, CH_2), 1.99 (ddd, $^2J_{C,H}$ = 14.9 Hz, $^3J_{C,H}$ = 7.2 Hz, $^3J_{C,H}$ = 4.3 Hz, 1 H, CH_2), 1.89 (ddd, $^2J_{C,H}$ = 14.9 Hz, $^3J_{C,H}$ = 6.9 Hz, $^3J_{C,H}$ = 4.4 Hz, 1 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1 (Cq), 128.5 (2 CH), 128.0 (CH), 127.8 (2 CH), 117.6 (CN), 73.5 (CH_2), 70.7 (Cq), 66.7 (CH_2), 38.8 (CH_2), 30.4 (quint., $^1J_{C,D}$ = 20.4 Hz, CD_2), 26.1 (quint., $^1J_{C,D}$ = 19.5 Hz, CD_2) ppm. MS (EI, 70 eV): m/z (%) = 224 (4) $[M]^+$, 195 (1), 182 (1), 163 (1), 119 (4), 107 (49), 91 (100), 79 (23), 65 (24), 46 (33), 39 (7). IR (ATR): $\tilde{\nu}$ = 3467 (br.), 3064 (w), 3032 (w), 2920 (w), 2869 (w), 2250 (w), 1496 (w), 1454 (w), 1416 (w), 1366 (m), 1097 (s), 1046 (m), 854 (w), 815 (w), 740 (m), 699 (m) cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε, L mol^{-1} cm^{-1}) = 227 (200), 258 (180) nm. HRMS (EI, 70 eV): calcd. for $C_{13}H_{12}D_5NO_2$ $[M]^+$ 224.15676; found 224.15669.

[2,2,6,6,6-$^2H_5$]mevalonolactone (1e): Compound **8e** (4.41 g, 19.7 mmol) was added to a suspension of Pd/Al_2O_3 (2.09 g, 1.96 mmol, 10 wt.% Pd) in ethanol (40 mL) in the presence of wet acetic acid (2 mL). The reaction was carried out in a stainless steel autoclave (HR-100, Berghof, Eningen) equipped with a magnetic stirrer in a hydrogen atmosphere at 60 °C. When no starting material was detected by TLC or GC analysis, the mixture was filtered and concentrated. Due to its instability, the crude product (1.62 g) was used immediately and without further purification in the next reaction. The oil was dissolved in D_2O (15 mL). To the mixture was added a solution of NaOD in D_2O (1.50 g, 40 wt.%, 15 mmol) and stirred for 20 h. The mixture was acidified with HCl (2 N), and the mixture was concentrated. The resulting residue was purified by column chromatography on silica gel with hexane/ethyl acetate (1:1) to give **1e** (1.23 g, 9.11 mmol, 46%) with no detectable loss of deuterium by ^{1}H NMR spectroscopy and GC–MS analysis. TLC (hexane/ethyl acetate, 1:1; R_f = 0.12). GC (BPX-5, MSTFA): I = 1384. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.58 (ddd, $^2J_{C,H}$ = 11.3 Hz, $^3J_{C,H}$ = 8.4 Hz, $^3J_{C,H}$ = 6.4 Hz, 1 H, CH_2), (ddd, $^2J_{C,H}$ = 11.3 Hz, $^3J_{C,H}$ = 5.0 Hz, $^3J_{C,H}$ = 4.2 Hz, 1 H, CH_2), 2.75 (br. s, 1 H, OH), 1.89 (dd, $^3J_{C,H}$ = 2.9, $^3J_{C,H}$ = 5.1 Hz, 1 H, CH_2), 1.88 (d, $^3J_{C,H}$ = 4.6 Hz, 1 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (CO), 67.8 (Cq), 66.1 (CH_2), 43.9 (quint., $^1J_{C,D}$ = 20.5 Hz, CD_2), 35.7 (CH_2), 28.7 (sept., $^1J_{C,D}$ = 18.6 Hz, CD_3) ppm. MS (EI, 70 eV, MSTFA): m/z (%) = 192 (10), 162 (6), 148 (100), 135 (4), 118 (37), 101 (11), 73 (31), 59 (6), 46 (16). IR (ATR): $\tilde{\nu}$ = 3415 (br.), 2974 (w), 2924 (w), 2227 (w), 1714 (s), 1475 (w), 1407 (m),

1278 (m), 1223 (m), 1149 (m), 1096 (m), 1048 (m), 992 (m), 959 (m), 927 (w), 892 (w), 803 (m), 742 (w), 651 (m) cm^{-1}.

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