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The source of oxygen in cerium-catalyzed α-hydroxylation of β-dicarbonyl compounds

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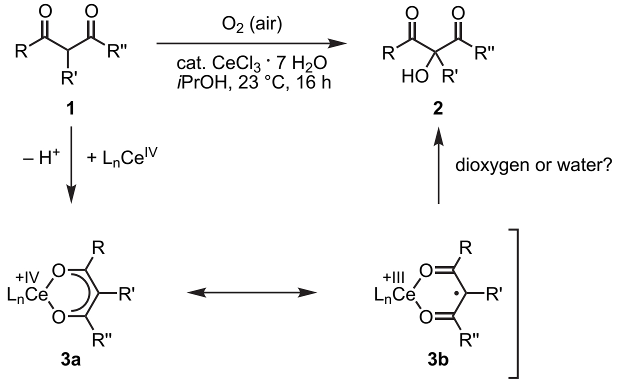
ABSTRACT

An investigation into the mechanism of the cerium-catalyzed α-hydroxylation of β-dicarbonyl compounds is presented. By ^{18}O-labeling studies it was proved that dioxygen is the direct source of the HO-groups in the product. It was excluded that the HO-groups originate from nucleophilic attack of water to an electrophilic radical intermediate. Based on these results and on the stoichiometry of the reaction, a new hypothesis for the mechanism is proposed.

1. Introduction

The direct α-oxidation of β-dicarbonyl compounds **1** is a very elegant access to α-hydroxy-β-dicarbonyl compounds **2**, a structural motif,[1] which is present in some natural products, but also appears on intermediate stages of natural product synthesis.[2] Several reagents were reported to achieve this α-hydroxylation,[1] newer reports utilize hydroperoxides with organocatalysis,[3] oxaziridines with Ni- or Zn-catalysis,[4] hydrogen peroxide with Fe-catalysis,[5] and molecular oxygen with Pd-catalysis.[6] Ce(IV) compounds are common reagents in organic synthesis and can be used in stoichiometric amounts to oxidize the α-position of a β-dicarbonyl compounds **1**.[7] More efficient is, however, the catalytic use of Ce-salts for the α-hydroxylation of β-dicarbonyl compounds **1** (Scheme 1).[8] The key feature of this reaction is the utilization of molecular oxygen (air) as oxidant, which can regarded to be optimal with respect to economic and ecological issues. Although Ce(III) alone cannot be oxidized by oxygen, oxidation to Ce(IV) is possible when Ce(III) is coordinated to β-dicarbonyl ligands. Moreover, the precatalyst $CeCl_3{\cdot}7H_2O$ is not toxic and inexpensive. The high efficiency of this method was already proved in the total synthesis of the natural products gmelinol **4**,[2a] stemonamin **5**,[2c] and kjellmanianone **2a** (Scheme 2).[9]

The detailed mechanism of this α-hydroxylation is still unclear. It is actually known from stoichiometrically used Ce(IV)-reagents, that reactions proceed via an α-radical like **3b** (Scheme 1). Formation of such species **3b** can be proposed as ligand-to-metal charge transfer from Ce(IV)-diketonato-complex **3a**. In the catalytic cycle, Ce(III) must be reoxidized to Ce(IV) by air. Obviously, coordination of Ce(III) to β-diketones or β-oxoesters shifts the redox potential and makes this air-oxidation possible. Malonates do, however, not coordinate readily to Ce(III), therefore this reaction sequence does not apply for the α-hydroxylation of malonates. We have recently tried to prove the radical character at α-carbon by transformation of α-cyclopropyl-β-dicarbonyl compounds, but no ring opening under reaction conditions was observed.[10] Nevertheless, the radical could be trapped with styrene yielding 1,2-dioxane derivatives.[11] This C–C bond forming process was meanwhile developed further for the synthesis of 1,4-diketones,[12] which are valuable starting materials for the synthesis of eight-membered ring lactams.[13]



Scheme 1. Ce-catalyzed α-hydroxylation of β-dicarbonyl compounds **1** and proposed reaction intermediates **3**.

Today we wish to report on our investigations on the source of the α-hydroxy group, which could be either dioxygen itself or

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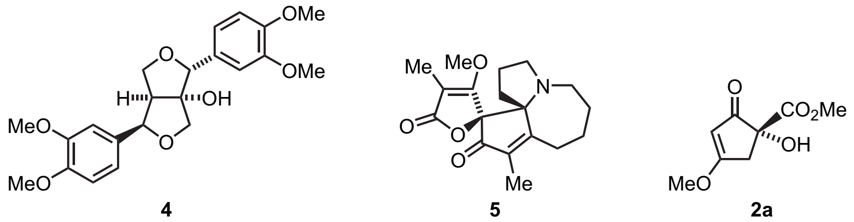
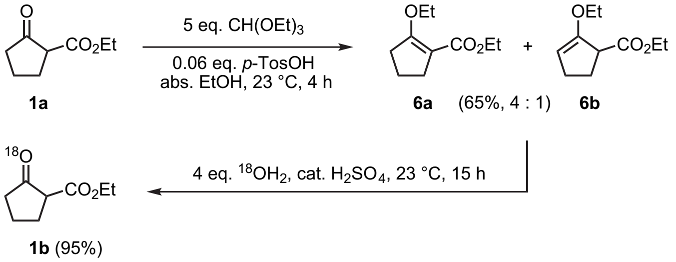


Scheme 2. Natural products prepared by Ce-catalyzed α-hydroxylation of β-dicarbonyl compounds with molecular oxygen as the key step.

water. The latter assumption is originating from the observation that high loads of halogen counterions in the reaction mixture result in the formation of α-halogenated by-products.[8–10] It could be that the α-hydroxy group in the products **2** is the result of a nucleophilic attack of water to an electrophilic species like **3b**. This hypothesis could be verified by running the reaction in the presence of ^{18}O-labeled water.

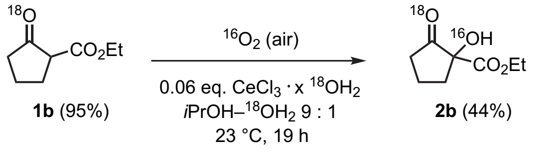
2. Results and discussion

In a first explorative experiment we oxidized oxoester **1a** with air in the presence of $^{18}OH_2$ and were able to detect ^{18}O incorporation already in the starting material. Obviously, ketones exchange oxygen with water in the presence of Lewis or Brönsted acids via the ketone hydrates. For this reason and in order to obtain univocal results, we pre-labeled the oxoester with ^{18}O in the ketone function by acid catalyzed hydrolysis of enolethers **6a** and **6b** with $^{18}OH_2$ (Scheme 3). Isotopomer **1b** was formed and isolated with quantitative selectivity and yield. The enolethers **6a** and **6b** were obtained according to a modified literature protocol[14] in 65% yield and in 4:1 ratio of regioisomers, which were not separated.



Scheme 3. Synthesis of ^{18}O-labeled oxoester **1b**.

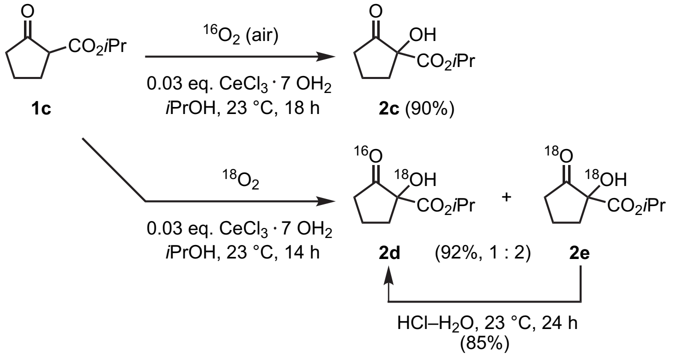
For the hydroxylation of labeled oxoester **1b** (1.0 equiv) dry, synthetic air was used (Scheme 4). The precatalyst $CeCl_3 \cdot \times {}^{18}OH_2$ was prepared by dissolving anhydrous $CeCl_3$ (0.06 equiv) in a small amount of $^{18}OH_2$ (1.3 equiv), which gave a solid hydrated material after cooling to ambient temperature. The solvent was a mixture of anhydrous *i*-PrOH and $^{18}OH_2$ (9:1). The conversion was followed by GC–MS and slow formation of mono-^{18}O-labeled **2b** (m/z=174) was observed. A molecular ion representing a double labeled isotopomer (m/z=176) of product **2b** was not detected. Conversion of starting material **1b** was complete after 19 h and product **2b** was isolated by chromatography. The yield is relatively low, because samples for GC analysis were taken from the reaction batch.



Scheme 4. α-Hydroxylation of labeled oxoester **1b** with air in the presence of $^{18}OH_2$.

We conclude without a doubt that water cannot be the source of the hydroxy function in product **2b**. Therefore, water is not taking part in the α-hydroxylation as a reactive component.

Oxidation reactions of oxoester **1a** (m/z=156) showed two minor (ca. 1–5%) components in the GC–MS spectra of the reaction mixture with m/z 170 and 186. Similarly, in the oxidation of isotopomer **1b** (m/z=158) two species with m/z=172 and 188 were observed. With $\Delta m/z$=14 we presumed small extent of transesterification reactions of starting materials leading to small amounts of isopropylester **1c** as well as the respective product **2c**. For this reason, we have prepared[15] and submitted isopropylester **1c** to Ce-catalyzed α-hydroxylation. Product **2c** was obtained in good yield after chromatography (Scheme 5). Comparison of authentic samples of isopropylesters **1c** and **2c** indeed confirmed the by-products observed in the experiments with ethyl esters **1a** and **1b**.



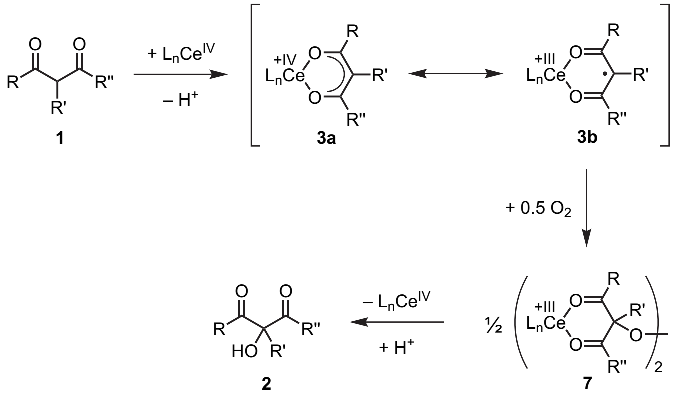
Scheme 5. α-Hydroxylation of isopropyl oxoester **1c** with normal air and with [^{18}O]-dioxygen.

In order to prove finally that dioxygen is the source of the hydroxy function in products **2** we planned to perform the oxidation reaction in an atmosphere of $^{18}O_2$ (Scheme 5). This gas was generated by electrolysis of $^{18}OH_2$ under strict exclusion of air and normal water and transferred into an evacuated Schlenk tube containing *i*-PrOH, oxoester **1c** and the catalyst. The reaction was not followed by GC, but interrupted after 14 h stirring at 23 °C. A mixture of isotopomeric hydroxyesters **2d** (m/z=188) and **2e** (m/z=190) (92% yield, ratio 1:2 by GC–MS) was obtained. Obviously, under reaction conditions $^{18}O_2$ is reduced to $^{18}OH_2$, the latter exchanges oxygen with the ketone moiety via the hydrate. In order to obtain an unique material, this product mixture was treated with diluted hydrochloric acid, and mono-labeled compound **2d** was obtained (85% yield) and fully characterized. It can be concluded that $^{18}O_2$ was definitely the source of isotope incorporation into the hydroxy group of product **2d**.

In summary, we conclude that the origin of the hydroxy group in the Ce-catalyzed α-oxidation of β-dicarbonyl compounds is not nucleophilic attack of water to an electrophilic species such as radical **3b** (as we speculated in earlier communications). The HO-group in the products must originate directly from dioxygen.

On the other hand, oxygen uptake measurements were performed by gravimetric as well as volumetric analysis: In a typical experiment, 85% conversion of 2.0 mmol starting material **1a** (i.e., formation of 1.7 mmol product) required a volume of 18 ml O_2 (i.e., 0.81 mmol at standard conditions) and a mass of 27 mg O_2 (i.e., 0.84 mmol). With an experimental error, this can be interpreted as the following stoichiometry: 2 equiv of oxoester **1c** react with 1 equiv of dioxygen. This excluded co-oxidation of another reaction component, e.g., the solvent isopropanol. And indeed, we failed to detect acetone in the reaction mixture by GC.

Although the detailed mechanism of this catalysis remains still unclear, we propose the following working model based on the stoichiometry and the fact that water does not play a role as reactant in the catalytic cycle (Scheme 6): β-Dicarbonyl compounds **1** are oxidized by Ce(IV)-species in solution to form Ce(III)-complexes **3b** with an unpaired electron at the α-position. The latter could form some kind of peroxo-species, for example, a dimer such as represented in formula **7**. The peroxo-moiety re-oxidizes 2 equiv of Ce(III) under formation of 2 equiv of hydroxylated products **2**. It is however unclear, if peroxo-species play a role in this mechanism and whether Ce coordinates to them. Other trivalent Lewis acids, like Sc(III), Yb(III), La(III) or Eu(III) compounds, do not perform this α-hydroxylation reaction, which makes the Ce(III)/Ce(IV) redox pair unique among all rare earth elements.



Scheme 6. Hypothesis on the mechanism being in accord with stoichiometry and role of dioxygen as the direct source of the hydroxy function.

3. Experimental section

3.1. General remarks

Preparative column chromatography was carried out using Merck SiO_2 (0.035–0.070 mm, type 60 A) with hexane and *tert*-butylmethylether (MTBE) as solvents. TLC was performed on Merck SiO_2 F_{254} plates on aluminum sheets. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 and Avance DPX 300. Multiplicities were determined with DEPT experiments. EIMS and HRMS spectra were obtained with a Finnigan MAT 95 spectrometer. GC–MS spectra were recorded with a Thermo Focus GC equipped with DSQ spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a 'GoldenGate' diamond-ATR unit. Electrolysis was performed with a potentiostat Zentro–Elektrik Pforzheim, LA75/1GA Nr. 2005 at U=75 V and at 0 °C. Isopropyl ester **1c**[15] was prepared according to a literature procedure. The preparation of enolethers **6a** and **6b** was adopted from the literature.[14] All other starting materials were commercially available. [^{18}O]-Water (97%) was purchased from Eurisotop.

*3.1.1. Ethyl 2-ethoxy-1-cyclopentene-1-carboxylate (**6a**) and 2-ethoxy-2-cyclopentene-1-carboxylate (**6b**).* *p*-TosOH (330 mg, 1.9 mmol, 0.06 equiv) was added to a mixture of oxoester **1a** (5.00 g, 32.0 mmol, 1 equiv), $CH(OEt)_3$ (23.7 g, 160 mmol, 5 equiv), and abs. EtOH (25 ml). The reaction mixture was stirred at 23 °C for 4 h, then directly submitted to vacuum distillation through a Vigreux column (15 cm). A mixture of both enolethers **6a** and **6b** (3.82 g, 20.7 mmol, 65%) was obtained at 135 °C (1.7 mbar) as a colorless liquid, ratio **6a**/**6b**=4:1 (by ^1H NMR). Isomer **6a**: ^1H NMR ($CDCl_3$, 300 MHz): δ=1.27 (t, J=7.1 Hz, 3H), 1.35 (t, J=7.1 Hz, 3H), 1.80–1.90 (m, 2H), 2.55 (ddt, J=7.7 Hz, J=7.3 Hz, J=1.8 Hz, 2H), 2.63 (ddt, J=7.9 Hz, J=7.5 Hz, J=1.8 Hz, 2H), 4.09 (q, J=7.0 Hz, 2H), 4.16 (q, J=7.1 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ=14.27 (CH_3), 15.27 (CH_3), 19.24 (CH_2), 29.08 (CH_2), 31.36 (CH_2), 59.06 (CH_2), 66.07 (CH_2), 103.98 (C), 165.15 (C), 168.49 (C) ppm. GC–MS (EI, 70 eV), m/z (%): 184 (10) $[M]^+$, 155 (12), 139 (27), 110 (100), 82 (25). Isomer **6b**: ^1H NMR ($CDCl_3$, 300 MHz): δ=1.26 (t, J=7.1 Hz, 3H), 1.28 (t, J=7.0 Hz, 3H), 2.06–2.24 (m, 2H), 2.25–2.35 (m, 1H), 2.40–2.51 (m, 1H), 3.41–3.48 (m, 1H), 3.81 (q, J=7.0 Hz, 2H), 4.12–4.20 (m, 2H), 4.61 (td, J=2.3 Hz, J=1.6 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ=14.07 (CH_3), 14.31 (CH_3), 26.37 (CH_2), 27.75 (CH_2), 49.89 (CH), 60.39 (CH_2), 65.06 (CH_2), 96.62 (CH), 156.49 (C), 174.03 (C) ppm. GC–MS (EI, 70 eV), m/z (%): 184 (12) $[M^+]$, 155 (29), 127 (7), 109 (100), 83 (70). Both isomers: IR (ATR): 2981 (m), 1735 (m), 1710 (m), 1683 (m), 1651 (m), 1628 (s), 1413 (m), 1381 (m), 1221 (s), 1148 (m), 1007 (m), 1053 (vs), 774 (m) cm^{-1}. HRMS (EI), calcd 184.1099 (for $C_{10}H_{16}O_3$); found 184.1101 $[M^+]$.

*3.1.2. [2-^{18}O]-Ethyl 2-oxocyclopentanecarboxylate **1b**.* Concentrated H_2SO_4 (5 mg, 5 μmol) was added under exclusion of air and moisture to an emulsion of a mixture of enolethers **6a** and **6b** (750 mg, 4.07 mmol) and [^{18}O]-water (410 mg, 20.4 mmol). The mixture was stirred at 23 °C for 15 h and subsequently neutralized with saturated $NaHCO_3$-solution (0.1 ml) and extracted four times with MTBE (4×1 ml). The combined organic layers were dried ($MgSO_4$), filtered, the solvent was removed in vacuo, and the residue was purified by chromatography on SiO_2 [hexane/MTBE 5:1 with gradient to 2:1, R_f=0.30 (hexane/MTBE 2:1)] to yield ^{18}*O*-labeled compound **1b** (612 mg, 3.87 mmol, 95%) as a colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.29 (t, J=7.1 Hz, 3H), 1.79–1.94 (m, 1H), 2.10–2.20 (m, 1H), 2.26–2.34 (m, 4H), 3.14 (t, J=8.9 Hz, 1H), 4.20 (q, J=7.1 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ=14.14 (CH_3), 20.94 (CH_2), 27.38 (CH_2), 38.02 (CH_2), 54.74 (CH), 61.32 (CH_2), 169.39 (C), 212.22 (C) ppm. IR (ATR): 2981 (m), 1736 (s), 1705 (vs), 1456 (m), 1371 (m), 1338 (m), 1300 (m), 1255 (s), 1190 (s), 1111 (s), 1026 (s), 931 (m), 836 (m) cm^{-1}. GC–MS (EI, 70 eV), m/z (%): 158 (6) $[M^+]$, 130 (63), 112 (73), 111 (69), 101 (34), 85 (26), 73 (100).

*3.1.3. [2-^{18}O]-Ethyl 1-hydroxy-2-oxocyclopentanecarboxylate **2b**.* A mixture of anhydrous $CeCl_3$ (50 mg, 0.20 mmol, 0.06 equiv) and [^{18}O]-water (81 mg, 4.0 mmol, 1.3 equiv) was heated for 5 min to 80 °C. After cooling to ambient temperature, this material was added to a solution of ^{18}*O*-labeled compound **1b** (500 mg, 3.16 mmol, 1.0 equiv) and *t*-BuPh (50 mg as internal standard for GC) in *i*-PrOH (1.8 ml) and [^{18}O]-water (0.2 ml). The mixture was then stirred at 23 °C for 19 h in an atmosphere of synthetic air. In certain time intervals, about 50 μl-samples were taken from the mixture and analyzed by GC–MS. Subsequently, the mixture was transferred on top of an SiO_2-column and separated by chromatography (hexane/MTBE 2:1). The ^{18}*O*-labeled alcohol **2b** (244 mg, 1.39 mmol, 44%) was obtained as the main fraction (R_f=0.19) and as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.29 (t, J=7.2 Hz, 3H), 2.05–2.17 (m, 3H), 2.43–2.53 (m, 3H), 3.50 (s, 1H), 4.26 (q, J=7.1 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ=14.00 (CH_3), 18.34 (CH_2), 34.72 (CH_2), 35.77 (CH_2), 62.48 (CH_2), 79.74 (C), 171.54 (C), 213.22 (C) ppm. IR (ATR): 3467 (m, br), 2981 (m), 1754 (s), 1731 (s), 1402 (m), 1368 (m), 1258 (m), 1166 (s), 1097 (m), 1020 (m), 861 (m) cm^{-1}. GC–MS (EI, 70 eV), m/z (%)=174 (33) [M$^+$], 146 (4), 128 (20), 118 (36), 116 (45), 101 (59), 100 (41), 90 (83), 88 (100), 70 (63).

*3.1.4. Isopropyl 1-hydroxy-2-oxocyclopentanecarboxylate (**2c**).* Oxoester **1c** (100 mg, 0.588 mmol) and $CeCl_3 \cdot 7H_2O$ (7 mg, 0.02 mmol) were suspended in *i*-PrOH (0.25 ml) and the mixture was stirred under an atmosphere of air at 23 °C for 18 h. After removal of all volatile materials in vacuo, the residue was purified by column chromatography (SiO_2, hexane/MTBE 5:1 with gradient to 2:1) to furnish alcohol **2c** (98 mg, 0.53 mmol, 90%) as the main fraction [R_f=0.18 (hexane/MTBE 2:1)] and as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.25 (d, J=6.3 Hz, 3H), 1.29 (d, J=6.3 Hz, 3H), 2.05–2.16 (m, 3H), 2.42–2.49 (m, 3H), 3.66 (s, 1H), 5.10 (hept, J=6.3 Hz, 1H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ=18.38 (CH_2), 21.46 (CH_3), 21.67 (CH_3), 34.70 (CH_2), 35.81 (CH_2), 70.63 (CH), 79.66 (C), 171.15 (C), 213.44 (C) ppm. IR (ATR): 3472 (w, br), 2981 (m), 2941 (w), 1754 (s), 1721 (s), 1375 (m), 1259 (m), 1173 (s), 1102 (vs), 910 (m) cm^{-1}. GC–MS (EI, 70 eV), m/z (%): 186 (1) [M$^+$], 144 (82), 126 (6), 116 (17), 99 (56), 88 (100), 70 (61). HRMS (EI): calcd 186.0892 (for $C_9H_{14}O_4$); found 186.0894 [M$^+$].

*3.1.5. [1-^{18}O]-Isopropyl 1-hydroxy-2-oxocyclopentanecarboxylate (**2d**) and [1,2-$^{18}O_2$]-isopropyl 1-hydroxy-2-oxocyclopentanecarboxylate (**2e**).* The reaction was performed under exclusion of moisture and air in a Schlenk tube. Oxoester **1c** (50 mg, 0.29 mmol) and $CeCl_3 \cdot 7H_2O$ (5 mg, 0.01 mmol) were suspended in abs *i*-PrOH (0.15 ml). The mixture was cooled with liquid N_2, evacuated, and from time to time $^{18}O_2$ was inserted, generated by electrolysis of $^{18}OH_2$ in a separate U-tube connected by inert gas flushed tubings. After stirring at 23 °C for 14 h, all volatile materials were removed in vacuum and the residue filtered through SiO_2 (hexane/MTBE 2:1) to furnish a mixture of mono and double labeled alcohols **2d** and **2e** (ratio 2:1 by GC–MS) (50 mg, 0.27 mmol, 92%) as a colorless oil. After addition of hydrochloric acid (c=1 mol dm^{-3}, 5 mg) and water (100 mg) to this product, the resulting mixture was then stirred at 23 °C for 1 day. Subsequently, it was transferred on top of an SiO_2-column and separated by chromatography (hexane/MTBE 5:1). Mono-labeled product **2d** (43 mg, 0.23 mmol, 79%) was obtained as the main fraction [R_f=0.22 (hexane/MTBE 2:1)] and as a colorless oil. GC–MS showed the isotopomers **2d** (83%) and **2c** (17%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.25 (d, J=6.3 Hz, 3H), 1.29 (d, J=6.3 Hz, 3H), 2.06–2.13 (m, 3H), 2.43–2.49 (m, 3H), 3.68 (s, 1H), 5.10 (hept, J=6.3 Hz, 1H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ=18.37 (CH_2), 21.45 (CH_3), 21.67 (CH_3), 34.69 (CH_2), 35.81 (CH_2), 70.63 (CH), 79.63 (C), 171.14 (C), 213.44 (C) ppm. IR (ATR): 3459 (w, br), 2982 (m), 2941 (w), 1755 (vs), 1727 (s), 1376 (m), 1260 (m), 1172 (s), 1104 (vs), 1004 (w), 910 (m) cm^{-1}. MS (EI, 70 eV), m/z (%): 188 (4) [M$^+$], 146 (70), 128 (6), 118 (7), 101 (52), 88 (100), 60 (40). HRMS (EI): calcd 188.0936 (for $C_9H_{14}{}^{16}O_3{}^{18}O$); found 188.0935 [M$^+$].

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