# An Efficient Large-Scale Synthesis of (*R*)-(–)-Mevalonolactone Using Simple Biological and Chemical Catalysts

Romano V. A. Orru,* Ingrid Osprian, Wolfgang Kroutil, Kurt Faber

Institute of Organic Chemistry, Graz University of Technology, Stremayrgasse 16, A-8010 Graz, Austria
Fax: +43(316)8738740; E-mail: romano@orgc.tu-graz.ac.at

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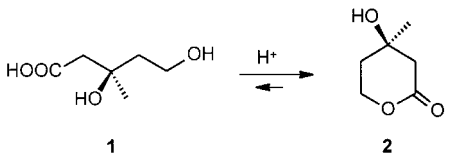
**Abstract:** Natural (*R*)-(–)-mevalonolactone **(2)** was synthesized in eight steps in 55% total yield and >99% ee employing an enantioconvergent chemoenzymatic route. In the key step, 2-benzyl-2-methyloxirane (±)-**3** was deracemized on a large scale (10 g) using lyophilized cells of *Nocardia* EH1 and sulfuric acid. The product diol (*S*)-**4** was isolated in 94% chemical yield and 94% optical purity.

**Key words:** mevalonolactone, epoxide hydrolase, chemoenzymatic synthesis, enantioconvergent

(*R*)-(–)-Mevalonic acid **(1)** is a key intermediate in a broad spectrum of cellular biological processes and their regulation.[1] Its significance as a biosynthetic precursor for terpenes, vitamins, and sterols has been clearly demonstrated. The transformation of 3-hydroxy-3-methylglutaryl CoA into mevalonate, catalyzed by HMG-CoA reductase, is a crucial step in the biosynthesis of cholesterol.[1] In medicine it is known that inhibition in the production of cellular **1** leads to lowering of plasma cholesterol.[2] This makes the biological formation of (*R*)-(–)-mevalonic acid **(1)** an important control site.[3a] The level of (*R*)-**1** in plasma and/or urine has been used to study the mechanisms and efficacy in the treatment of hyperlipidemias, and the efficacy of lovastatin as an anticancer agent.[3] Thus, both for diagnostic and therapeutic reasons, simple and cheap access to natural mevalonic acid **(1)** is of significant value. As such **1** or, more particularly, its cyclic lactone form **2** (Scheme 1) has been a synthetic target of considerable interest. Folkers and co-workers isolated **2** and elucidated its structure.[4] The naturally occurring (–)-isomer has the (*R*)-configuration which was shown by correlation of the (+)-enantiomer with (–)-quinic acid.[5] Cornforth and co-workers were the first to prepare both enantiomers in essentially 100% ee from (+)- and (–)-linalool.[6] Since then a number of asymmetric syntheses of (*R*)-(–)-mevalonolactone **(2)** have been reported. Among the chemical routes the most important employ the Sharpless asymmetric epoxidation,[7] which is a stereodifferentiating reaction, as well as those routes exploiting starting materials from the chiral pool.[8] A different and highly enantioselective approach is based on transcription of chirality from a chiral template.[9] Biocatalysts have also been used for the preparation of **2**. (*R*)-(–)-Mevalonolactone **(2)** may be produced via fermentation,[10] via procedures involving lipase-catalyzed kinetic resolutions,[11] or via hydrolysis of a prochiral diester employing esterases.[12] A more recently published method includes a chloroperoxidase-catalyzed epoxidation of 3-methylbut-3-enoate.[13]

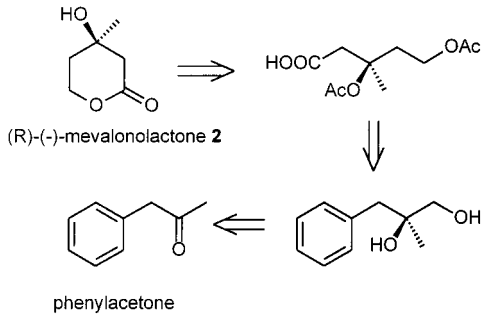
However, most of these methods make use of expensive reagents, are environmentally unsound, or are not applicable on a large scale. In the present paper we wish to describe a chemoenzymatic route that does not incur these drawbacks and yields (*R*)-(–)-mevalonolactone **(2)** efficiently.




**Scheme 1**

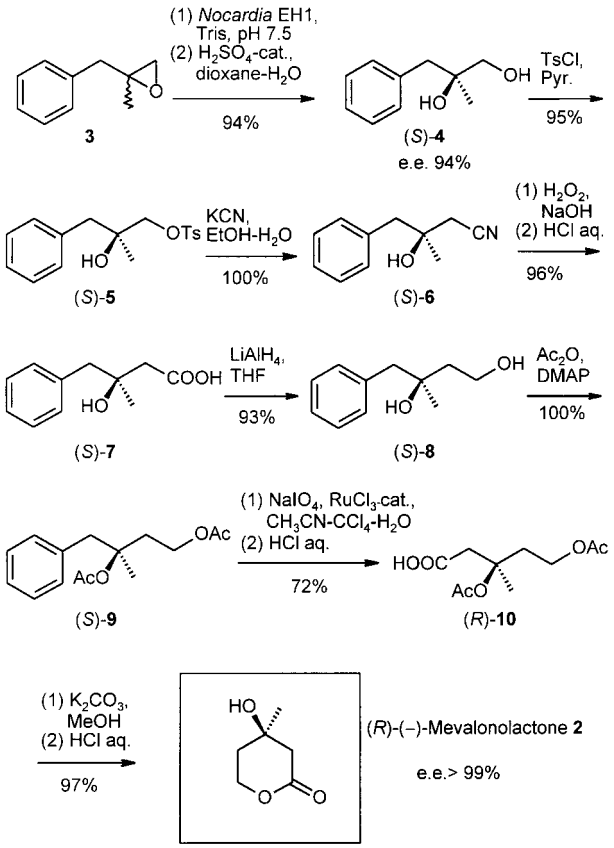
2,2-Disubstituted epoxides serve as suitable substrates for a recently developed enantioconvergent chemoenzymatic deracemization reaction.[14] This process proceeds via a socalled resolution-inversion sequence. Hydrolysis of (±)-epoxides catalyzed by a bacterial epoxide hydrolase proceeds via a classical kinetic resolution pattern.[15] The biotransformation reaction shows *retention* of configuration at the stereogenic center and produces a mixture of (*R*)-epoxide and (*S*)-diol.[16] Directly following the biohydrolysis, the remaining (*R*)-epoxide is hydrolyzed selectively by simple acid catalysis yielding the (*S*)-diol with complete *inversion*. In this way racemic 2,2-disubstituted oxiranes were selectively deracemized to give the corresponding (*S*)-1,2-diols in high chemical and optical yields.[14]

Substrates possessing a polar carboxy moiety relatively close to the oxirane ring are not accepted by the bacteria available, though an aryl functionality is lipophilic enough to be tolerated by the epoxide hydrolase.[17] Thus, 2-benzyl-2-methyloxirane **[**(±)-**3]**, prepared from readily available phenylacetone and trimethylsulfoxonium iodide,[17] is selectively hydrolyzed by lyophilized cells of *Nocardia* EH1 exhibiting strong epoxide hydrolase activity.[14] At this point we envisaged that the phenyl moiety might serve as a masked carboxylate functionality for a total synthesis of (*R*)-(–)-mevalonolactone **(2)** (Scheme 2).




**Scheme 2**

In general, oxiranes are believed to be toxic to living cells.[17] For example the *Nocardia* sp. dies within 72 hours upon incubation with (±)-**3**. Furthermore, compound **3** is not very soluble in the buffer system required for optimum activity and selectivity of the biocatalyst. This was believed to be problematic for a large-scale biotransformation of **3**.[18] To enhance solvation of the substrate which would promote the biohydrolysis reaction, a range of organic cosolvents at different concentrations were tested.[19] To our disappointment the enzymatic activity was lost and no hydrolysis products were detected at all. Apparently the epoxide hydrolase is deactivated in the solvent systems tested. At this point we decided to perform the large-scale biohydrolysis in plain buffer without any organic cosolvent. In order to keep the reaction manageable, the buffer volume relative to the amount of substrate and biocatalyst was decreased considerably as compared to the analytical scale reaction.[17] Furthermore, the enzymatic hydrolysis was performed at a slightly elevated temperature in order to speed up the reaction. In this way (±)-**3** could be resolved with high selectivity (E = 123)[20] into (*R*)-**3** and (*S*)-**4** on a large scale (10 g) within 48 hours. These results support a recent semiempirical model for enzymatic suspension reactions,[21] which suggests that the process time in such cases can only be accelerated by increasing the substrate solubility through raising the temperature and not through the addition of organic cosolvents.




**Scheme 3**

Direct coupling of the acid-catalyzed *inversion* reaction to the biocatalytic resolution went smoothly. Accordingly, a mixture of (*R*)-**3** and (*S*)-**4** was treated with 93% aqueous $H_2SO_4$ as catalyst in dioxane from which the diol (*S*)-**4** could be isolated in 94% yield and 94% ee. An efficient procedure for the large-scale preparation of the key intermediate had been established, and the synthesis of natural mevalonolactone could be completed (Scheme 3).

The primary hydroxy group of (*S*)-**4** was tosylated (TsCl, pyridine) and after crystallization enantiopure (*S*)-**5** was obtained in 95% yield. Chain elongation was achieved quantitatively by treatment of the tosylate with KCN in EtOH/$H_2O$. Carboxylic acid (*S*)-**7** was then formed in high yield from nitrile (*S*)-**6** using strongly basic $H_2O_2$. Alternatively, the same transformation could be performed under much milder (neutral) conditions employing a chemoselective biocatalyst with nitrile-hydrolyzing activity (*Rhodococcus* R312).[22] The carboxylate function of (*S*)-**7** was reduced with $LiAlH_4$ in refluxing THF to give diol (*S*)-**8** in 93% isolated yield. Subsequent acetylation employing neat acetic anhydride and a catalytic amount of 4-dimethylaminopyridine (DMAP) afforded quantitatively the diacetate (*S*)-**9**. From literature it became clear that the oxidation of the aryl moiety to a carboxylate using ruthenium tetroxide[8a,23] was to be prefered over ozonolysis[23b] (poor yields). However, in our hands the excellent yields under the conditions reported elsewhere[8a] could not be reproduced. After closely monitoring the course of the reaction it was found that the formation of (*R*)-**10** was complete within 5 minutes after the addition of a catalytic amount of fresh ruthenium trichloride. It should be emphasized that the ruthenium catalyst was added, at once, to a refluxing biphasic water/acetonitrile/$CCl_4$ (2:1:1) solvent mixture containing the aryl compound and sodium metaperiodate. Immediate workup (to prevent overoxidation) gave 72% of pure carboxylic acid (*R*)-**10**. Simple saponification followed by acidic lactonization afforded enantiopure (>99% ee) natural (*R*)-(−)-mevalonolactone **(2)**, which was isolated in 55% overall yield starting from racemic **3**.

This represents the first application of a bacterial epoxide hydrolase in a large-scale total synthesis. The key intermediate was formed in ca. 10 g in an enantioconvergent way via simple combination of bio- and acid catalysis. As such, this procedure provides a new tool which can be used in the syntheses of chiral intermediates and/or optically active natural products.

Melting points are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ , unless otherwise noted, on a Bruker MSL 300 at 300 and 75.47 MHz, respectively. Chemical shifts are relative to TMS ($\delta$ = 0.00) with $CHCl_3$ as an internal standard [$\delta$ = 7.23,$^1H$ and 76.90, $^{13}C$]. $^{13}C$ NMR multiplicities were determined by using a DEPT pulse sequence. MS were recorded at 70 eV via DI-EI on a KRATOS-profile spectrometer. FT-IR spectra were recorded on a Bomem-Michelson M100 spectrometer as a neat film on a NaCl disc. Optical rotation values were measured on a Perkin-Elmer 341 polarimeter at 589 nm (Na line) in a 1 dm cuvette at 20°C. The reaction course was routinely monitored by TLC (Merck 60 $F_{254}$) and the products were visualized

by spraying with vanillin/$H_2SO_4$, Mo-reagent, or $KMnO_4$-reagent. Carboxylic acids were visualized using a bromocresol green/bromophenol blue/$KMnO_4$ spray.[24] Alternatively, reactions were followed by GC analysis carried out on a Shimadzu GC-14A equipped with FID and a RSL 1701 capillary column (30m, 0.25 mm, 0,25 µm film, $N_2$). Enantiomeric excesses were analyzed on the same gas chromatograph using a CP-Chirasil-DEX CB column (25m, 0.32 mm, 0.25 µm film, $H_2$). Flash chromatography was performed on silica gel Merck 60 (230–400 mesh). Petroleum ether had a boiling range of 60–90 °C.

Solvents were dried and freshly distilled by standard techniques. For anhydrous reactions, flasks were dried overnight at 150 °C and flushed with dry argon just before use, and reactions were carried out under argon. Organic extracts were dried over $Na_2SO_4$, and then the solvent was evaporated under reduced pressure. The bacterial strain of *Nocardia* EH1 was a gift from J. de Bont (Wageningen, The Netherlands) and C. Syldatk (Stuttgart, Germany), and was grown as previously described.[17]

**(*S*)-(–)-2-Methyl-3-phenylpropane-1,2-diol (4):**
Epoxide (±)-**3** (10.0 g, 67.7 mmol) was added to a suspension of rehydrated lyophilized whole cells of *Nocardia* EH1 (8.00 g)[25] in Tris-buffer (250 mL, 0.05 M, pH 7.5). The mixture was agitated at 35 °C and 125 rpm. At exactly 50% conversion (48 h) the mixture was continuously extracted with $CH_2Cl_2$ (500 mL, 36 h). The organic layer was washed with brine (100 mL), dried, and evaporated. To a stirred solution of the resulting bright orange oil (12.3 g) in dioxane (225 mL) was added dropwise 93% aq $H_2SO_4$ (18 mL) at 0 °C. The reaction mixture was stirred for 15 min at r.t. after which the acid was neutralized with satd aq $NaHCO_3$ solution. EtOAc (300 mL) was added, and the resulting biphasic mixture was stirred vigorously for an additional 30 min. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers were dried and concentrated. Flash chromatography of the residue (petroleum ether/EtOAc, 2:1) afforded **4** as white crystals; yield: 10.5 g (94%); ee 94%. Spectroscopic, physical and optical data of **4** were in full agreement with those previously reported.[14b,17]

**(*S*)-(+)-2-Methyl-3-phenylpropane-1,2-diol 1-(*p*-Toluenesulfonate) (5):**
To a stirred solution of diol **4** (5.00 g, 30.1 mmol) in pyridine (250 mL) was added TsCl (9.00 g, 47.0 mmol). The solution was stirred for 18 h at r.t. and concentrated. Aq $CuSO_4$ solution (20% w/v, 150 mL) and EtOAc (200 mL) were then added and the mixture was stirred for 30 min at r.t. The aqueous layer was extracted with EtOAc (3 × 75 mL) and the combined organic phases were washed with brine (50 mL), dried and evaporated. Crystallization (diisopropyl ether) of the crude material gave **5**; yield: 9.15 g (95%); mp 134 °C (dec); $[\alpha]_D$ +9.2 (*c* = 5, $CHCl_3$).
IR: $\nu$ = 3497, 3029, 2956, 1596, 1361, 973, 824, 737, 702 $cm^{-1}$.
$^1H$ NMR: $\delta$ = 1.10 (s, 3 H), 2.01 (s, 1 H), 2.45 (s, 3 H), 2.75 (d, 1 H, *J* = 13.5 Hz), 2.83 (d, 1 H, *J* = 13.5 Hz), 3.81 (s, 2 H), 7.10-7.28 (m, 5 H), 7.36 (d, 2 H, *J* = 8.6 Hz) 7.82 (d, 2 H, *J* = 8.2 Hz).
$^{13}C$ NMR: $\delta$ = 21.73 ($CH_3$), 23.80 ($CH_2$), 44.49 ($CH_3$), 71.42 ($CH_2$), 75.06 (C), 126.92 (CH), 128.09 (2 × CH), 128.41 (2 × CH), 130.04 (2 × CH), 130.45 (2 × CH), 132.32 (C), 135.90 (C), 145.17 (C).
MS: *m/z* (%) = 229 ($M^+$–91, 66), 155 (77), 135 (22), 91 (100), 65 (18), 43 (21).
HRMS: *m/z* calc. for $C_{10}H_{13}SO_4$ ($M^+$–91) 229.05346, found 229.05294.

**(*S*)-(+)-3-Hydroxy-3-methyl-4-phenylbutanonitrile (6):**
The tosylate **5** (9.15 g, 28.6 mmol) was dissolved in a mixture of EtOH/$H_2O$ (60% v/v, 150 mL) and stirred at 0 °C. KCN (4.00 g, 61.5 mmol) was added and the solution was allowed to warm to r.t. After stirring for 18 h the solution was concentrated, brine (100 mL) was added, the mixture was extracted with $CH_2Cl_2$ (5 × 50 mL), and the combined organic layers were dried and evaporated. Flash chromatography (petroleum ether/EtOAc, 1:2) gave **6** as a white solid; yield: 5.01 g (~100%); mp 101–102 °C (hexane/EtOAc, 1:9); $[\alpha]_D$ +8.3 (*c* = 0.5, 90% EtOH).
IR: $\nu$ = 3436, 2977, 2922, 2254, 1493, 1450, 1112, 744, 702 $cm^{-1}$.
$^1H$ NMR: $\delta$ = 1.38 (s, 3 H), 2.19 (s, 1 H), 2.47 (s, 2 H), 2.92 (s, 2 H), 7.22–7.39 (m, 5 H).
$^{13}C$ NMR: $\delta$ = 26.94 ($CH_3$), 30.65 ($CH_2$), 47.28 ($CH_2$), 71.21 (C), 117.78 (C), 127.33 (CH), 128.73 (2 × CH), 130.41 (2 × CH), 135.75 (C).
MS: *m/z* (%) = 175 ($M^+$, 4), 160 (2), 142 (8), 135 (18), 91 (100), 84 (9), 65 (22), 43 (31).
HRMS: *m/z* calc. for $C_{11}H_{13}NO$ ($M^+$) 175.09971, found 175.09909.

**(*S*)-(–)-3-Hydroxy-3-methyl-4-phenylbutanoic acid (7):**
Nitrile **6** was hydrolyzed with basic $H_2O_2$ (Method A) or with *Rhodococcus* R312 (Method B):

*Method A:* A mixture of NaOH (100 mL, 3 M) and $H_2O_2$ (40 mL, 30%) was added to the hydroxy nitrile **6** (3.50 g, 18.0 mmol). The reaction mixture was heated at 65 °C for 1 h and then refluxed for an additional hour, after which the temperature of the mixture was allowed to lower to r.t. and then further cooled to 0 °C. HCl (6 M) was then added until a pH < 3 was reached. The resulting suspension was extracted with $Et_2O$ (5 × 25 mL) and the combined $Et_2O$ layers were dried and concentrated to afford pure **7** as a strong smelling oil which solidified below 20 °C; yield: 3.36 g (96%); $[\alpha]_D$ –2.4 (*c* = 5, abs EtOH).
IR: $\nu$ = 3605–2885, 1709, 1600, 1494, 1452, 1214, 744, 702 $cm^{-1}$.
$^1H$ NMR (acetone-$d_6$): $\delta$ = 1.25 (s, 3 H), 1.41 (s, 1 H), 2.45 (s, 2 H), 2.89 (s, 2 H), 7.17–7.31 (m, 5 H), 7.51–7.94 (br s, 1 H).
$^{13}C$ NMR (acetone-$d_6$): $\delta$ = 27.44 ($CH_3$), 45.22 ($CH_2$), 48.49 ($CH_2$), 72.01 (C), 127.22 (CH), 128.81 (2 × CH), 131.68 (2 × CH), 138.75 (C), 174.35 (C).
MS: *m/z* (%) = 194 ($M^+$, 0.5), 143 (3), 135 (12), 103 (51), 92 (100), 85 (43), 65 (22), 43 (63).
HRMS: *m/z* calc. for $C_{11}H_{14}O_3$ ($M^+$) 194.09429, found 194.09429.

*Method B:* Nitrile **6** (1.00 g, 5.72 mmol) was added to a suspension of rehydrated lyophilized whole cells of *Rhodococcus* R312[22] (1.25 g) in Tris-buffer (25 mL, 0.05 M, pH 7.5). The mixture was agitated at 30 °C and 120 rpm until the starting material was consumed (24 h). Then the pH was adjusted to just below 3 with HCl (6 M) and the remaining cell material was precipitated by centrifugation at 10000 g for 15 min. The aqueous suspension was decanted and extracted with $Et_2O$ (4 × 20 mL). The combined organic phases were dried and evaporated. The resulting orange oil was chromatographed (EtOAc) on a silica column treated with AcOH (5%) to give pure **7**; yield: 0.74 g (67%); $[\alpha]_D$ –2.2 (*c* = 5, abs EtOH).

**(*S*)-(–)-3-Methyl-4-phenyl-1,3-butanediol (8):**
A solution of acid **7** (3.00 g, 15.5 mmol) in anhyd THF (75 mL) was added slowly to a refluxing suspension of $LiAlH_4$ (0.75 g, 19.7 mmol) in anhyd THF (15 mL). The mixture was refluxed for 1 h, then cooled to 0 °C. Excess $LiAlH_4$ was quenched with satd aq $NH_4Cl$ solution (20 mL), the salts were dissolved by adding HCl (5 mL, 6 M) and the aqueous layer was extracted with EtOAc (6 × 25 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (25 mL), dried and concentrated. Flash chromatography (petroleum ether/EtOAc, gradient from 3:1 to 1:1) gave **8** as a clear oil; yield: 2.59 g (93%); $[\alpha]_D$ –2.0 (*c* = 5, abs EtOH).
IR: $\nu$ = 3476–3027, 2937, 1602, 1493, 1452, 1113, 1054, 761, 701 $cm^{-1}$.
$^1H$ NMR: $\delta$ = 1.20 (s, 3 H), 1.61–1.89 (s, 2 H), 2.75 (d, 1 H, *J* = 13.1 Hz), 2.86 (d, 1 H, *J* = 13.1 Hz), 2.96 (br s, 1 H), 3.43 (br s, 1 H), 3.88 (dd, 2 H, *J* = 5.3, 6.3 Hz), 7.18–7.31 (m, 5 H).
$^{13}C$ NMR: $\delta$ = 26.47 ($CH_3$), 41.68 ($CH_2$), 48.93 ($CH_2$), 59.65 ($CH_2$), 73.76 (C), 126.58 (CH), 128.23 (2 × CH), 130.68 (2 × CH), 137.29 (C).

MS: *m/z* (%) = 162 ($M^+$–18, 4), 135 (26), 117 (12), 91 (62), 71 (32), 65 (17), 43 (100).
HRMS: *m/z* calc. for $C_{11}H_{14}O$ ($M^+$-18) 175.09971, found 175.09909.

**(*S*)-(−)-1,3-Diacetoxy-3-methyl-4-phenylbutane (9):**
$Ac_2O$ (100 mL) containing DMAP (0.75 g) was added to diol **8** (2.50 g, 13.8 mmol). The stirred solution was heated at 95 °C and after the reaction was complete (4 h) poured into ice water (250 mL). The mixture was stirred for another 2 h and then extracted with $CH_2Cl_2$ (5 × 50 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ solution (3 × 50 mL) and brine (50 mL), dried, and concentrated (eventually at 60 °C/0.09 Torr). The resulting strong smelling brown oil was flash chromatographed (petroleum ether/EtOAc, 3:1) to give **9** as a clear viscous oil; yield: 3.67 g (~100%); $[\alpha]_D$ −8.5 (*c* = 5, abs EtOH).
IR: $\nu$ = 2941, 1734, 1451, 1368, 1240, 1031, 734, 703 $cm^{-1}$.
$^1H$ NMR: $\delta$ = 1.44 (s, 3 H), 2.00 (s, 3 H), 2.05 (s, 3 H), 2.17-2.39 (m, 2 H), 3.06 (d, 1 H, *J* = 13.7 Hz), 3.23 (d, 1 H, *J* = 13.7 Hz), 4.20 (t, 2 H, *J* = 7.0 Hz), 7.15-7.36 (m, 5 H).
$^{13}C$ NMR: $\delta$ = 21.05 ($CH_3$), 22.49 ($CH_3$), 23.92 ($CH_3$), 36.71 ($CH_2$), 44.68 ($CH_2$), 60.63 ($CH_2$), 82.79 (C), 126.71 (CH), 128.17 (2 × CH), 130.61 (2 × CH), 136.60 (C), 170.66 (C), 171.08 (C).
MS: *m/z* (%) = 205 ($M^+$–59, 11), 173 (10), 144 (98), 129 (61), 91 (62), 71 (50), 43 (100).
HRMS: *m/z* calc. for $C_8H_{13}O_4$ ($M^+$–91) 173.08138, found 173.08148 and calc. for $C_{11}H_{12}$ ($M^+$–120) 144.09390, found 144.09235.

**(*R*)-(−)-3,5-Diacetoxy-3-methylbutanoic Acid (10):**
The diacetate **9** (2.20 g, 8.33 mmol) was dissolved in a mixture of MeCN (50 mL), $CCl_4$ (50 mL) and distilled water (100 mL). The vigorously stirred mixture was heated to reflux temperature. Subsequently, $NaIO_4$ (56.0 g, 260 mmol) and fresh $RuCl_3$ hydrate (0.25 g, 1.20 mmol)[26] were added. The colour changed from black via orange to yellow within 5 min, after which the heterogenous mixture was poured into a mixture of $CH_2Cl_2$ (150 mL) and ice water (150 mL). After stirring for 30 min, the pH of the mixture was adjusted to 10 with aq NaOH (3 M) and the mixture was extracted with $CH_2Cl_2$ (2 × 50 mL). The aqueous layer was acidified with concd HCl (pH < 3) and extracted with EtOAc (10 × 50 mL). The combined EtOAc extracts were dried and evaporated to give pure **10** as a strong smelling yellow oil; yield: 1.39 g (72%); $[\alpha]_D$ −3.6 (*c* = 1, abs EtOH).
IR: $\nu$ = 3675–2685, 1734, 1722, 1430, 1370, 1243, 1026 $cm^{-1}$.
$^1H$ NMR: $\delta$ = 1.59 (s, 3 H), 2.01 (s, 3 H), 2.04 (s, 3 H), 2.08–2.22 (m, 1 H), 2.32–2.46 (m, 1 H), 2.95 (d, 1 H, *J* = 15.0 Hz), 3.12 (d, 1 H, *J* = 15.1 Hz), 4.15–4.23 (m, 2 H), 8.11–8.94 (br s, 1 H).
$^{13}C$ NMR: $\delta$ = 20.99 ($CH_3$), 22.23 ($CH_3$), 24.43 ($CH_3$), 37.03 ($CH_2$), 42.54 ($CH_2$), 60.22 ($CH_2$), 79.90 (C), 170.62 (C), 171.14 (C), 175.57 (C).
MS: *m/z* (%) = 217 ($M^+$–15, 0.5), 173 (2), 155 (4), 145 (7), 112 (28), 87 (12), 71 (20), 43 (100).
HRMS: *m/z* calc. for $C_8H_{13}O_4$ ($M^+$–59) 173.08138, found 173.08102 and calc. for $C_6H_9O_4$ ($M^+$–87) 145.05008, found 145.05008.

**(*R*)-(−)-Mevalonolactone (2):**
To a stirred solution of **10** (1.30 g, 5.60 mmol) in MeOH (125 mL) was added $K_2CO_3$ (5.00 g, 35.0 mmol). The mixture was refluxed overnight, then the MeOH was evaporated and $H_2O$ (200 mL) was added. The resulting solution was cooled to 0 °C, acidified to pH 1 with concd HCl, and continuously extracted with $CHCl_3$ (250 mL, 18 h). The organic phase was dried, evaporated and flash chromatographed (EtOAc) to give pure **2**; yield: 0.71 g (97%); ee > 99%; $[\alpha]_D$ −23.7 (*c* = 4, abs EtOH) [Lit.[6] $[\alpha]_D$ −23 (*c* = 6, abs EtOH)].
IR: $\nu$ = 3392, 2944, 1717, 1396, 1252, 1126, 1069 $cm^{-1}$.
$^1H$ NMR: $\delta$ = 1.38 (s, 3 H), 1.87–1.94 (m, 2 H), 2.38–2.64 (br s, 1 H), 2.50 (d, 1 H, *J* = 17.8 Hz), 2.66 (d, 1 H, *J* = 17.6 Hz), 4.28–4.39 (m, 1 H), 4.53–4.66 (m, 1 H).
$^{13}C$ NMR: $\delta$ = 29.74 ($CH_3$), 35.89 ($CH_2$), 44.72 ($CH_2$), 66.14 ($CH_2$), 68.19 (C), 170.42 (C).
MS: *m/z* (%) = 130 ($M^+$, 4), 115 (6), 85 (10), 71 (92), 58 (51), 43 (100).
HRMS: *m/z* calc. for $C_6H_{10}O_3$ ($M^+$) 130.06299, found 130.06268.

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EtOAc, *t*-BuOH, THF, dioxane, isopropyl alcohol, acetone, acetonitrile, DMF, DMSO, MeOH, and ethylene glycol.
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