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Practical enantioselective synthesis of fully deuterated (*R*)-mevalonolactone

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Abstract—Practical enantioselective synthetic method of fully deuterated (*R*)-mevalonolactone has been developed based upon Sharpless asymmetric epoxidation. (*R*)-Mevalonolactone-d_9 **1** was prepared on multi-gram scale in seven steps in 17% overall yield.

1. Introduction

Isoprenoids are biosynthesized by consecutive condensations of their five-carbon precursor, isopentenyl diphosphate, to the isomeric starter, dimethylallyl diphosphate. Two pathways for these precursors are known. One is the so-called mevalonate pathway,[1] which operates in eucaryotes, archaea, and cytosols of higher plants. The other is a recently discovered pathway, the non-mevalonate pathway, which is used by eubacteria, green algae, and chloroplasts of higher plants.[2] (*R*)-Mevalonate is the essential and first biosynthetic precursor in the mevalonate pathway to varieties of isoprenoids such as various vertebrate- and invertebrate hormones, membrane-anchors of proteins including oncogene products, membrane core lipids of archaea, visual pigments, vitamins and an enormous number of terpenoids in microorganisms, plants and animals.[3] Since the isotope-tracer methodology is vital for diverse aspects of research in this field, various isotopomers of racemic[4] and chiral[5] mavalonate and mavalonolactone have been prepared to date, and tritium and/or deuterium as tracers are usually used for stereochemical analysis of terpenoid biosynthesis. However, it is also conceivable that protium can be utilized to track hydrogen when the background protium can be significantly reduced.

Along this line, we previously reported the enantioselective synthesis of (*R*)-mevalonolactone-d_9 using chirality control on a carbohydrate template.[6] However, synthetic efficiency must be further improved for practical use. We recently devised an easy and convenient method for the gram scale synthesis of mevalonolactone-d_9 in a racemic form.[7] This methodology may well be meritorious for mechanistic enzymology, particularly, the key transformation involving proton attack and/or proton quench in the studies of terpene biosynthesis. In fact, by using this racemic perdeuterated mevalonolactone-d_9, straightforward stereochemical analysis of isoprenoid biosynthesis has recently been demonstrated as well by labeling experiments and ^{1}H NMR spectroscopy.[8] However, development of efficient synthetic methodology for chiral version of fully deuterated mevalonate is apparently desirable for these type of feeding experiments on the view point of molecular economy. In this paper, we describe an enantioselective and practical synthesis of chiral mevalonolactone-d_9 (**1**) on multi-gram scale.

2. Results and discussion

The enantioselective synthesis of fully deuterated mevalonolactone was based on our previous synthesis of racemic mevalonate-d_9[7] as shown in Scheme 1. First, both of two precursors, 3,4-dimethoxyphenylacetone-d_5 **2**[7] and triethyl phosphonoaceate-d_2 **3**[9] were prepared by simple exchange reaction of the non-deuterated counterparts with ^2H_2O in the presence of K_2CO_3. Horner–Emmons reaction between the deuterated precursor **2** and the deuterated phosphonoacetate **3**, instead of previously employed methyl ester derivative,[7] proceeded smoothly to give ester **4** as a mixture of geometrical isomers (*E*/*Z*=5.5). The geometry of the deuterated α,β-unsaturated ester **4** was determined by comparison of ^{1}H and ^{13}C NMR with non-labelled compound. A crucial improvement was the use of ethyl ester instead of methyl ester, thus, a geometrical ratio was improved from *E*/*Z*=3 to 5.5, and importantly the major *E*-isomer was obtained in crystalline form. Thus, recrystallization from hexane gave a pure *E*-isomer **4** in 59% yield. The

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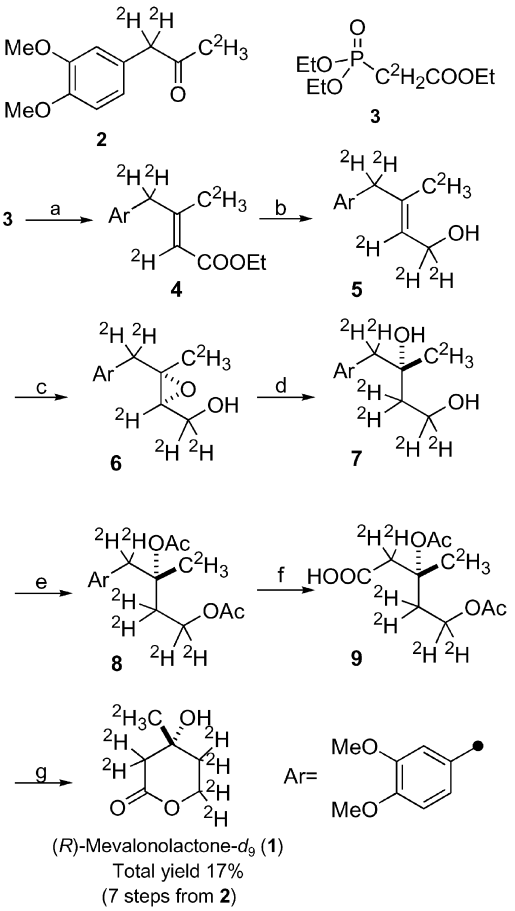

Scheme 1. Synthesis of mevalonolactone-d_9 **1**. (a) NaH, THF, then **2**, and then recrystallization, 59%. (b) $LiAl^2H_4$, ether, 74%. (c) TBHP, (L)-(+)-DIPT, $Ti(OiPr)_4$, CH_2Cl_2, and then recrystallization, 77%. (d) $LiAl^2H_4$, THF, 86%. (e) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 99%. (f) $RuCl_3$, $NaIO_4$, CCl_4–CH_3CN–H_2O, 71%. (g) K_2CO_3–MeOH, and then H_3O^+, 86%.

resulting *E*-ester **4** was subsequently reduced with $LiAl^2H_4$ to afford allylic alcohol **5** in 74% yield. Under these reduction conditions, the saturated alcoholic product derived from the 1,4-addition of deuteride and reduction of the ester function was formed along with the desired allylic alcohol.

The desired allylic alcohol **5** was next subjected to the asymmetric Sharpless epoxidation[10] with *t*-butyl hydroperoxide, (L)-(+)-diisopropyl tartrate, and $Ti(OiPr)_4$, in CH_2Cl_2 to yield epoxide **6**. The enantiomeric purity of the epoxide **6** was determined to be 92% ee by ^{19}F NMR analysis of its (+)-MTPA ester derivative (major isomer; $\delta_F=-72.96$, minor isomer $\delta_F=-73.04$ in $CDCl_3$-d_6). When (L)-(+)-diethyl tartrate was used instead of (L)-(+)-diisopropyl tartrate, enantiomeric excess was as low as 80%. Fortunately, the resulting expoxide **6** was obtained again in crystalline form and the enatiomeric excess was further improved to >99% ee by recrystallization from ethyl acetate. Further reduction of **6** with $LiAl^2H_4$ easily afforded the desired diol **7** in 86% yield. Two hydroxyl groups were then protected as acetate **8** under standard conditions. Ruthenium oxidation[11] of **8** proceeded smoothly, and carboxylic acid **9** was obtained in good yield; $[\alpha]_D=-2.8$ (*c* 0.97, ethanol), [lit., $[\alpha]_D=-3.6$ for non-labelled compound].[12] Deprotection and final extraction under acidic conditions afforded the desired (*R*)-mevalonolactone-d_9 **1** in 17% overall yield in seven steps.

The structure of mevalonolactone-d_9 was confirmed by spectroscopic data and the absolute configuration was confirmed by its optical rotation; $[\alpha]_D=-20.5$ (*c* 6.13, ethanol), [lit., $[\alpha]_D=-25.6$,[12a] -23.7,[12] -22,[13b] -17.6,[13c] -21.6,[13d] -20,[13e] -23,[13f] -23.4,[13g] -23,[13h] -19.9[13i] for non-labelled compound]. The deuterium contents of the synthesized **1** were estimated by ^1H NMR to be 96, 99, 99, and 97% at C-2, C-4, C-5, and the methyl group, respectively. In summary, we have successfully developed a multi-gram scale synthetic method for highly optically active and fully deuterated (*R*)-mevalonolactone.

3. Experimental

3.1. General

Deuteriochloroform (99.8% atom ^2H, Merck) was used as the solvent for ^1H and ^{13}C NMR spectra, unless otherwise stated. ^1H, ^2H, ^{19}F and ^{13}C NMR chemical shifts were reported in δ values based on internal TMS (δ_H 0), a solvent signal ($CHCl_3$: δ_D 7.26, $CDCl_3$: δ_C 77.0) or external CF_3COOH (δ_F −77.0) as references. *J* values are given in hertz. Elemental analyses were performed with a Perkin–Elmer 2400 apparatus. Column chromatography was carried out with Kieselgel 60 (63–200 mesh, Merck). All reactions were carried out in an argon atmosphere. THF and ether were distilled from sodium/benzophenone ketyl prior to use. CH_2Cl_2 and pyridine were distilled from P_2O_5 and potassium hydroxide, respectively. Deuterium oxide (99.8% atom ^2H) and $LiAl^2H_4$ (99% atom ^2H) were purchased from Merck and Isotec Inc., respectively.

3.1.1. Triethyl phosphono[2,2-$^2H_2$]acetate (3). To a mixture of triethyl phosphonoacetate (60.0 g, 268 mmol) and deuterium oxide (17.3 g, 865 mmol), K_2CO_3 (1.08 g, 7.8 mmol) was added. The solution was stirred for 1.5 h at room temperature and was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated to dryness. This procedure was repeated five times to give **3** (56.9 g, quant.). ^1H NMR (270 MHz): δ 1.29 (t, *J*=7.2 Hz, 3H), 1.35 (t, *J*=7.0 Hz, 6H), 4.18 (dq, *J*=8.1, 7.0 Hz, 4H), 4.20 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (75 MHz): δ 13.60, 15.84, 33.59 (double quintet, *J*=132.8, 19.2 Hz), 62.09, 62.17, 165.12.

3.1.2. Ethyl (*E*)-3-[$^2H_3$]methyl-4-(3,4-dimethoxyphenyl)-[2,4,4-$^2H_3$]but-2-enoate (4). Tetrahydrofuran (350 ml) was added to pre-washed sodium hydride (7.1 g, 178 mmol), and then **3** (42.3 g, 187 mmol) was added portionwise at 0°C. The mixture was stirred for 1 h at room temperature. A solution of **2** (34.9 g, 175 mmol) in THF (160 ml) was then added at 0°C. The resulting mixture was stirred for 7 h at room temperature. Then, acetic acid (7.5 ml) and water (20 ml) were added, and the mixture was extracted four times with EtOAc. The combined organic layer was washed with $NaHCO_3$ aq and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography with hexane–EtOAc (5:1–1:1) to give oily ester (41.8 g, 89%) as a geometrical mixture (*E*/*Z*=ca. 5.5). Recrystallization of the mixture from hexane gave a pure *E*-isomer **4** (27.8 g,

59%). Mp 47.2–49.0°C; ^{1}H NMR (270 MHz): δ 1.27 (t, J=7.2 Hz, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.15 (q, J=7.2 Hz, 2H), 6.65–6.82 (m, 3H); ^{13}C NMR (75 MHz): δ 13.73, 17.07 (septet, J=19.4 Hz), 45.17 (quintet, J=19.3 Hz), 55.17, 58.88, 110.69, 111.69, 116.09 (t, J=23.3 Hz), 120.72, 129.58, 147.29, 148.43, 157.88, 165.94; IR ($CHCl_3$): 1628, 1705 cm^{-1}. Anal. calcd for $C_{15}H_{14}{}^2H_6O_4$: C, 66.63; H+^{2}H, 7.45. Found: C, 66.78; H+^{2}H, 7.15.

3.1.3. (*E*)-5-(3,4-Dimethoxyphenyl)-3-[$^2H_3$]methyl-2-[1,1,2,4,4-$^2H_5$]pent-2-en-1-ol (5). To a suspension of lithium aluminum deuteride (2.75 g, 65.4 mmol) in ether (212 ml), a solution of **4** (17.7 g, 65.4 mmol) in ether (176 ml) was added at 0°C. The mixture was stirred at 0°C for 2.5 h. Water (2.7 ml), 15% NaOH aq (2.7 ml), and water (8.1 ml) were successively added at 0°C. The insoluble matter was filtered and washed with EtOAc. The filtrate and washings were combined, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by silica gel column chromatography with hexane–EtOAc (5:1–1:1) to give **5** (11.2 g, 74%), which contained ca. 8% saturated alcohol. This was used for the next step without further purification. ^{1}H NMR (270 MHz): δ 3.86 (s, 6H), 6.67–6.81 (m, 3H); ^{13}C NMR (75 MHz): δ 14.71 (septet, J=19.2 Hz), 44.41 (quintet, J=20.0 Hz), 55.41, 55.47, 57.93 (quintet, J=20.9 Hz), 110.77, 111.78, 120.54, 124.41 (t, J=25.4 Hz), 131.68, 137.91, 147.00, 148.38; IR ($CHCl_3$): 1644, 2102, 2200, 3410 cm^{-1}. Anal. calcd for $C_{13}H_{10}{}^2H_8O_3$: C, 67.78; H+^{2}H, 7.87. Found: C, 67.54; H+^{2}H, 8.11.

3.1.4. (2*S*,3*S*)-2,3-Epoxy-5-(3,4-dimethoxyphenyl)-3-[$^2H_3$]methyl-[1,1,2,2,4,4-$^2H_5$]pentan-1-ol (6). Titanium tetraisopropoxide (9.4 ml, 31.8 mmol, 110 mol%) and (L)-(+)-diisopropyl tartrate (6.67 ml, 31.7 mmol, 110 mol%) were added to a mixture of powdered molecular sieves 4A (14 g) in CH_2Cl_2 (152 ml) at −25°C, and the mixture was stirred for 30 min at the same temperature. A solution of **5** (6.70 g, 29.1 mmol) in CH_2Cl_2 (90 ml) was added dropwise, followed by a solution of ^{t}BuOOH (5–6 M solution in decane, 11.6 ml). The mixture was stirred at −25°C for 1 h. An aqueous 10% tartaric acid solution (66 ml) was added, and the matter was filtered and washed with CH_2Cl_2. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2, The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The residue was dissolved in ether (166 ml), and 1N NaOH aq (55 ml) was added at 0°C. The mixture was stirred at 0°C for 30 min and the organic layer was separated. The aqueous phase was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography with hexane–EtOAc (5:1–1:1) to give **6** (6.39 g) as colorless solid. Recrystallization of the solid from EtOAc gave crystalline **6** (5.48 g, 77%). Mp 79.9–81.1°C; $[\alpha]_D^{26}$=−8.44 (c 1.00, $CHCl_3$); ^{1}H NMR (270 MHz): δ 3.87 (s, 3H), 3.88 (s, 3H), 6.72–6.82 (m, 3H); ^{13}C NMR (75 MHz): δ 15.56 (septet, J=19.3 Hz), 41.83 (quintet, J=18.9 Hz), 55.52, 60.20 (quintet, J=22.2 Hz), 60.56, 61.28 (t, J=25.4 Hz), 109.73, 112.31, 121.25, 128.90, 147.45, 148.42; IR ($CHCl_3$): 2105, 2223, 3450 cm^{-1}. Anal. calcd for $C_{13}H_{10}{}^2H_8O_4$: C, 63.37; H+^{2}H, 7.36. Found: C, 63.56; H+^{2}H, 7.47.

3.1.5. (*S*)-5-(3,4-Dimethoxyphenyl)-3-[$^2H_3$]methyl-[1,1,2,2,4,4-$^2H_6$]pentane-1,3-diol (7). To a suspension of lithium aluminium deuteride (1.75 g, 41.7 mmol) in THF (78 ml), a solution of **6** (9.33 g, 37.9 mmol) in THF (97 ml) was added at 0°C. The mixture was stirred at room temperature for 2.5 h. Water (1.75 ml), 15% NaOH aq (1.75 ml), and water (5.25 ml) were successively added at 0°C. The insoluble matter was filtered and washed with EtOAc. The filtrate and washings were combined, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by silica gel column chromatography with hexane–EtOAc (1:1–1:2) to give **7** (8.63 g) as colorless solid. Recrystallization of the solid from EtOAc gave crystalline **7** (8.29 g, 86%). Mp 91.8–93.0°C; $[\alpha]_D^{27}$=−6.03 (c 1.09, $CHCl_3$); ^{1}H NMR (300 MHz): δ 2.56 (br, 1H), 3.06 (br, 1H), 3.87 (s, 6H), 6.72–6.83 (m, 3H); ^{13}C NMR (75 MHz): δ 25.36 (septet, J=18.5 Hz), 40.30 (quintet, J=19.1 Hz), 47.19 (quintet, J=18.5 Hz), 55.52, 58.34 (quintet, J=21.6 Hz), 72.89, 110.62, 113.57, 122.29, 129.54, 147.30, 148.10; IR ($CHCl_3$): 2110, 2225, 3350 cm^{-1}. Anal. calcd for $C_{13}H_{11}{}^2H_9O_4$: C, 62.61; H+^{2}H, 8.08. Found: C, 62.73; H+^{2}H, 8.20.

3.1.6. (*S*)-1,3-Diacetoxy-5-(3,4-dimethoxyphenyl)-3-[$^2H_3$]-methyl-[1,1,2,2,4,4-$^2H_6$]pentane (8). To a solution of **7** (6.73 g, 26.9 mmol) and DMAP (856 mg, 7.0 mmol) in CH_2Cl_2 (65 ml), Et_3N (10.5 ml, 75.3 mmol) was added. Then, acetic anhydride (16.8 ml, 178 mmol) was added at 0°C. The mixture was stirred for 44 h at room temperature. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ aq and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography with hexane–EtOAc (5:1–3:1) to give **8** (8.88 g, 99%) as an oil. $[\alpha]_D^{26}$=−1.32 (c 0.90, $CHCl_3$); ^{1}H NMR (300 MHz): δ 2.00 (s, 3H), 2.05 (s, 3H), 3.87 (s, 6H, 6.69–6.82 (m, 3H); ^{13}C NMR (75 MHz): δ 20.67, 22.16, 22.63 (septet, J=20.4 Hz), 35.34 (quintet, J=18.7 Hz), 42.97 (quintet, J=18.2 Hz), 55.48, 59.55 (quintet, J=21.6 Hz), 82.20, 110.53, 113.34, 122.36, 128.60, 147.48, 148.12, 170.22, 170.65; IR ($CHCl_3$): 1728, 2386, 3658 cm^{-1}. Anal. calcd for $C_{17}H_{15}{}^2H_9O_6$: C, 61.23; H+^{2}H, 7.26. Found: C, 61.34; H+^{2}H, 7.32.

3.1.7. (*R*)-3,5-Diacetoxy-3-[$^2H_3$]methyl-[1,1,2,2,4,4-$^2H_6$]-pentanoic acid (9). To a mixture of **8** (8.35 g, 25.0 mmol) and $NaIO_4$ (96.8 g, 45.3 mmol) in CCl_4 (57 ml), CH_3CN (57 ml), and phosphate buffer (90 ml, pH=7), $RuCl_3{\cdot}nH_2O$ (171 mg) was added at 0°C. The mixture was stirred below 20°C for 1 h, and then ether (50 ml) was added. The mixture was filtered through a pad of celite and the residue was washed with CH_2Cl_2. The organic layer of the filtrate and washings were combined, and concentrated to dryness. The residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (50:1–10:1) to give **9** (4.26 g, 71%) as an oil. $[\alpha]_D^{26}$=−2.8 (c 0.97, ethanol); ^{1}H NMR (300 MHz): δ 2.01 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz): δ 20.78, 22.01, 23.28 (septet, J=19.1 Hz), 35.93 (quintet, J=19.7 Hz), 41.93 (quintet, J=19.3 Hz), 59.42 (quintet, J=21.7 Hz), 79.40, 170.53, 171.09, 175.21; IR ($CHCl_3$): 1732, 2131, 2243, 2364, 2672, 3435, 3467, 3502, 3587, 3670 cm^{-1}. Anal. calcd for $C_{10}H_7{}^2H_9O_6$: C, 49.77; H+^{2}H, 6.68. Found: C, 47.53; H+^{2}H, 6.75.

3.1.8. (*R*)-Mevalonolactone-d_9 (1). To a solution of **9** (3.64 g, 15.0 mmol) in methanol (58 ml), K_2CO_3 (3.52 g, 25.0 mmol) was added. The mixture was stirred at room temperature for 2.5 h. 2 M HCl was added to make pH 7, and methanol was evaporated *in vacuo*. Then, 2 M HCl was added again to pH 2. The mixture was stirred at room temperature for 10 h. The resulting solution was extracted several times with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography with ether to give **1** (1.79 g, 86%) as an oil. $[\alpha]_D^{21}=-20.5$ (*c* 6.13, ethanol); ^{1}H NMR (300 MHz): δ 1.9 (br, 1H); ^{13}C NMR (100 MHz): δ 28.47 (septet, J=19.1 Hz), 34.63 (quintet, J=19.3 Hz), 43.81 (quintet, J=19.4 Hz), 65.65 (quintet, J=23.0 Hz), 67.50, 171.59; ^{2}H NMR (61 MHz, $CHCl_3$): δ 4.59 (1×^{2}H), 4.30 (1×^{2}H), 2.60 (1×^{2}H), 2.48 (1×^{2}H), 1.82 (2×^{2}H), 1.30 (3×^{2}H); IR ($CHCl_3$): 1716, 2121, 2227, 3434, 3600, 3670 cm^{-1}. Anal. calcd for $C_6H_1{}^2H_9O_3$: C, 51.76; H+^{2}H, 7.24. Found: C, 51.51; H+^{2}H, 7.51.

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