Short, Enantioselective Synthesis of Mevalonic Acid

Ryan J. Oconnell,[1] Nicholas J. Dolphin,[1] Olaf Wiest,[1*] and Paul Helquist[1*]

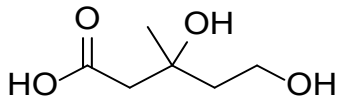
Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, 46556 USA

ABSTRACT A new enantioselective synthesis of mevalonic acid that is short, flexible, scalable to gram amounts, and uses readily available starting materials is reported. Enantioselective homoallylic epoxidation of isoprenol followed by enantiomeric enrichment gave the key epoxide intermediate. Further reactions led to either racemic mevalonic acid in 74% yield over two steps or the individual (*R*)- or (*S*)-enantiomer on a gram scale in 51% overall yield and ≥99% ee over five linear steps.

Introduction

Mevalonate is a key intermediate in the biosynthesis of many important compounds including cholesterol and other isoprenoids[1] through the mevalonate pathway that converts acetyl-CoA into isopentenyl pyrophosphate, which is then branched into several biosynthetic pathways.[2] The rate limiting step of the mevalonate pathway is a two-stage reduction of hydroxymethyl glutaryl-CoA (HMG-CoA) by the NADH-dependent enzyme HMG-CoA reductase (HMGR) to produce (*R*)-mevalonate.[3] As a result of this central role of mevalonate in isoprenoid synthesis, it has many applications, ranging from a tool in biochemical research through potential treatments of dermatitis to skin moisturizers.[4-5] Ongoing studies of the mechanism of HMGR in our group[1, 6-

[8] required large quantities of both the natural (*R*)-mevalonic acid **1** and its (*S*)-enantiomer. For this reason, we required a scalable synthesis that would give highly stereopure mixtures of either enantiomer of mevalonic acid, ideally using readily available starting materials and reagents.



Mevalonic acid **1**

Previous efforts towards the enantioselective synthesis of **1** used enzymatic reactions in order to impart stereochemical control,[9-11] which provides only one of the desired stereoisomers. Given the need for larger amounts of **1**, significant efforts have previously focused on bioengineering to improve mevalonate production by microbial fermentation.[12] Alternatively, substrates such as geraniol and linalool were used for either the chemical synthesis of racemic mevalolactone or for strategies with stereocontrol.[13-18] Following the development of the Sharpless epoxidation,[19] enantioselective routes involving epoxidation of allylic alcohols were developed.[20-23] This approach also enabled the chemical synthesis of partial and completely deuterated derivatives of the corresponding δ-lactone, mevalolactone, for the study of mevalonate biosynthesis.[24-25] The chemical syntheses involved a combination of many steps, low yields, and sub-95% ee product mixtures. For example, one of the most efficient, highest yielding syntheses begins with a Grignard reaction of allyl bromide and ethyl acetate leading to mevalolactone in four steps with a yield of 57%, but produces only a racemic product mixture.[26] Among the most efficient, highest % ee yielding synthetic strategies, the enzyme chloroperoxidase is used to impart chirality with an overall four-step synthesis and a 40% yield with 93% ee.[10] Although several routes with >95% ee have been reported,[9, 11, 13, 17, 20-21, 27] they typically involve many steps with low overall yield and/or rely on the use of substrates that are not readily available. For example,

Shimizu, *et al.* used a stereoselective epoxidation on the convex face of an enone system, followed by a retro Diels-Alder leading to (*R*)-mevalolactone with >99% ee but an overall yield of 13% over many steps.[13] Here, we present a short, efficient, scalable, and highly enantioselective synthesis of (*R*)-mevalonic acid which can also easily be tuned to produce (*S*)-mevalonic acid.

Results and Discussion

Our synthetic strategy begins with isoprenol, an inexpensive, commercially available compound. We first tested the viability of this route in a racemic synthesis (Figure 1). Epoxidation of isoprenol, followed by cyanide addition and *in situ* nitrile hydrolysis, gave (*R*/*S*)-**1** in 74% yield over two steps comprised of three reactions in a route that could easily be scaled to gram amounts. A similar ring opening of a different epoxide was used in a synthesis of mevalolactone.[10]

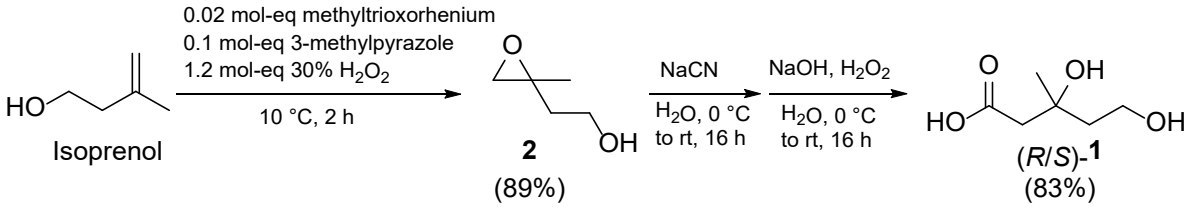


Figure 1. Racemic synthesis of mevalonic acid (*R*/*S*)-**1**.

For the enantioselective version of this synthesis, we tested different transition metal catalysts that have been reported for the enantioselective epoxidation of isoprenol with high % ee.[28-29] While a hafnium/diamine catalyst was reported to give 97% ee for this specific case,[28] we observed a low yield and 45% ee in our studies. More promisingly, a zirconium catalyst with diisopropyl L-tartrate ligands (L-DIPT)[29] was found to give a reproducibly high yield up to 87% and a % ee of 82% (Figure 2).

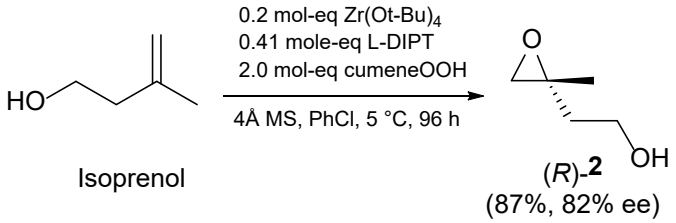


Figure 2. Zirconium-catalyzed enantioselective epoxidation.

The % ee of the product was determined through derivatization of the resulting epoxy alcohol **2** as a Mosher ester **S1** (Figure S1). Steglich esterification[30] of (*S*)-Mosher acid[31] with **2** produced a mixture of diastereomers that are quantifiable by ^{19}F NMR. ^{19}F NMR analysis of a racemic mixture of epoxide **2** (*S*)-Mosher ester derivatives produced two fully resolved peaks of equal height and integration (Figure S2A). The absolute stereochemistry of the epoxide **2** mixture obtained from use of the zirconium/L-DIPT catalyst was found to have a negative optical rotation, consistent with the reported (*R*)-stereoisomer.[28] Analysis of the Mosher ester **S1** by ^{19}F-NMR indicated an 82% ee (Figure S2B).

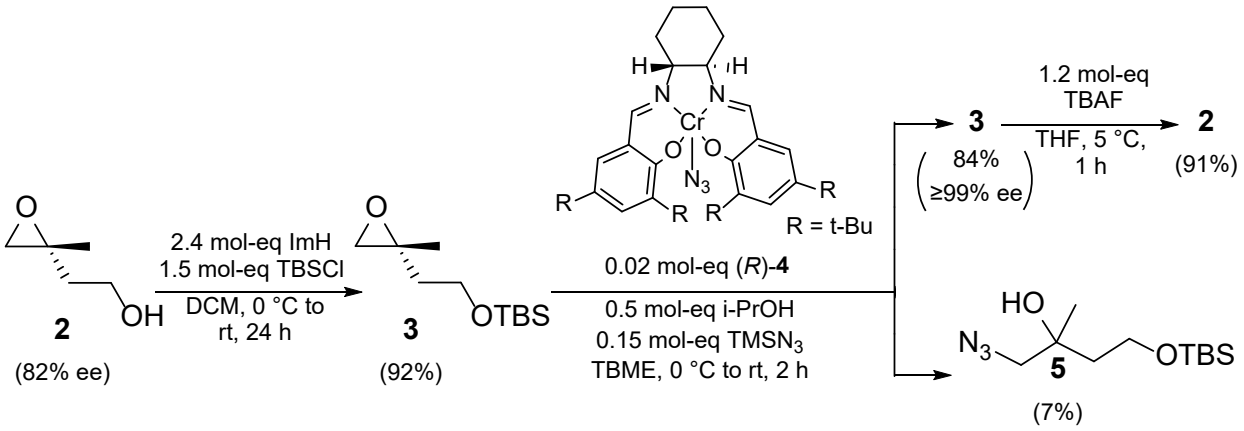


Figure 3. Kinetic resolution of epoxide **2**.

Although the 82% ee could be consistently reproduced on a gram scale, the enantiopurity was not sufficient for our purposes. The unwanted (*S*)-enantiomer was removed from the mixture by a kinetic resolution using a chromium-salen catalyst (*R*)-**4** described by Jacobsen and coworkers.[32] The primary alcohol of **2** was protected as a tert-butyldimethylsilyl (TBS) ether **3** in 92% yield. Reaction with 0.15 mol-equiv of TMS azide and the chromium-salen catalyst gave stereo-enriched **3** in an 84% recovered yield and azide **5** followed by TBS deprotection of **3** to give (*R*)-**2** in 91% yield (Figure 3). The enantiopurity of **2** was determined by the Mosher ester method described above. The peak corresponding to the minor stereoisomer was not observed (Figure S2C). Based upon determination of a detection limit of 0.5% (Figure S3), which is consistent with detection limits of 0.2-1% for ^{19}F NMR spectroscopy,[33] (*R*)-**2** was obtained with ≥99%.ee.

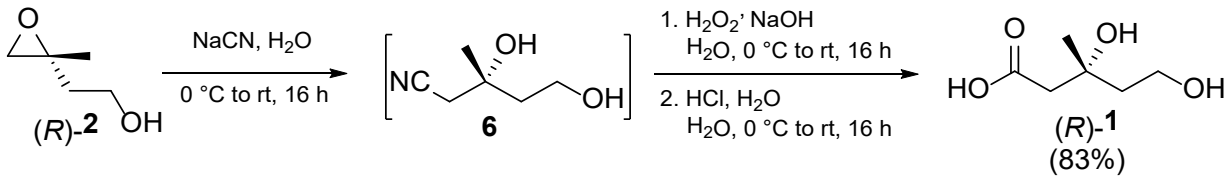


Figure 4. Synthesis of (*R*)-mevalonic acid (*R*)-**1** from epoxide **2**.

Synthesis of mevalonic acid **1** from epoxide **2** involved the addition of cyanide followed by base-catalyzed hydrolysis of the nitrile group of intermediate **6** as shown in Figure 4. Epoxide ring-opening regioselectivity followed a predictable pattern of attack on the least sterically hindered carbon under alkaline conditions.[34] As a result, (*S*)-epoxide **2** resulted in (*S*)-mevalonic acid, and (*R*)-epoxide **2** will resulted in (*R*)-mevalonic acid (see below). To circumvent challenges in the workup leading to low yields, intermediate **6** was carried through with hydrogen peroxide-promoted hydrolysis under alkaline conditions to give mevalonic acid **1** as an oil containing residual water. It is important to limit the amount of water used in this step as in case of a large

ratio of water to reactants, it was found that 2-methyl-1,2,4-butanetriol becomes a notable byproduct in the epoxide addition step. Additionally, excess cyanide was found to result in residual cyanide in the final product mixture. Under alkaline conditions with peroxide, the residual cyanide is converted into cyanate, which upon lowering of the pH decomposes into water, CO_2 and ammonia.[35] 1.2 Mol-equiv of cyanide was found to give optimal results for product formation and cyanide decomposition. In order to determine the yield, dimethyl sulfone was used as an internal integration standard for ^{1}H NMR, which indicated consistently high yields of 80-83% for multi-gram scale reactions such as an 83% yield for a 1.5-gram scale reaction. Although the conversion of (*R*)-**2** to (*R*)-**1** was not expected to result in any loss of configuration, the stereochemical integrity of this pathway was confirmed by NMR analysis of a Mosher ester derivative of (*R*)-**1** (Figure S4-6).

For synthesis of (*S*)-mevalonic acid, the procedure for (*R*)-mevalonic acid was repeated using the enantiomeric catalyst D-DIPT for the homoallylic epoxidation, followed by (*S*)-Mosher acid derivatization to ester **S1**. ^{19}F NMR indicated an 82% ee of the (*S*)-stereoisomer (Figure S7B). For kinetic resolution, enrichment of the (*S*)-epoxide utilized the Jacobsen catalyst enantiomer (*S*)-**4** synthesized by way of the (*S*,*S*)-Jacobsen's ligand, followed by TBS deprotection and (*S*)-Mosher acid derivatization. The resulting ^{19}F NMR again did not show a peak for the minor diastereomer, indicating a near total depletion of the (*R*)-stereoisomer (Figure S7C) and ≥99% ee. This sample of (*S*)-enriched epoxide was used for tandem nitrile addition/hydrolysis to give (*S*)-mevalonic acid **1**. To confirm no notable loss in configuration of the (*S*)-mevalonic acid mixture, ^{13}C NMR analysis of pHP-derivatized ester **S3** with Eu(hfc)$_3$ indicated the absence of a peak for its stereoisomer (Figure S8B). This is consistent with essentially stereopure (*S*)-mevalonic acid.

Conclusions

Herein, we have reported both a racemic and enantioselective synthesis of the biologically relevant mevalonic acid along with a facile method for % ee determination. This synthesis is amenable to gram-scale use with 51% yield of ≥99% ee (*R*)-mevalonic acid over 5 linear steps comprised of 6 reactions. This route has also been shown to be straightforwardly modified to give (*S*)-mevalonic acid by utilizing the enantiomers of the catalysts used for the epoxidation and Jacobsen resolution steps. With this synthetic strategy, large quantities of enantioenriched mevalonic acid can be synthesized for uses relevant to biological studies. Additionally, mevalonic acid itself can be used as a reactant for constructing more complex compounds as demonstrated by esters **S2** and S**3**. Therefore, this synthetic method can hopefully assist in advancing future biological and synthetic research.

Experimental

All reagents and solvents were obtained from Sigma Aldrich or VWR International. Deionized water was used in all cases of water utilization. Flash column chromatography was performed using a Biotage Isolera Prime system with Silicycle Inc. Siliasep cartridges. ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained using a Bruker AVANCE III HD 400 instrument operating at 400 MHz, 100 MHz, and 376 MHz respectively. All ^{1}H and ^{13}C data are reported in ppm (δ) relative to residual $CDCl_3$ (7.26 ppm, ^{1}H NMR; 77.23 ppm, ^{13}C NMR), CD_3OD (4.78 ppm, ^{1}H NMR; 49.15 ppm, ^{13}C NMR), and D_2O (4.79 ppm, ^{1}H NMR), and peaks were reported as br = broad signal, s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectrometry measurements were conducted with electrospray ionization (ESI) using a Bruker micrOTOF-Q II spectrometer. For infrared spectroscopy, a Jasco FT/IR-6300 instrument was used.

Compounds and Procedures:

(*R*/*S*)-2-(2-Methyloxiran-2-yl)ethan-1-ol (2)

Isoprenol (1.75 g, 20.3 mmol) was added to a RBF along with a stir bar and argon. The flask was placed in a 10 °C ice bath, and 3-methylpyrazole (170 mg, 2.1 mmol) was added along with methyltrioxorhenium (10 mg, 0.04 mmol). Then 30% H_2O_2 (2.76 mL, 24.4 mmol) was added dropwise, and the mixture was vigorously stirred at 10 °C for 2 h. Brine (40 mL) and EA (40 mL) were added, and the solution was transferred to a separatory funnel. The organic layer was separated and dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was loaded onto silica gel, and the product was purified with a gradient of Hex/EA to give racemic epoxide **2** as a clear, colorless oil (1.85 g, 89% yield). R_f = 0.5 (100% EA) $KMnO_4$ stain. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 (m, 2H), 2.75 (d, 1H, J = 4.3 Hz), 2.59 (d, 1H, J = 4.4 Hz), 2.53 (br, 1H) 1.83 (m, 2H), 1.33 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 59.32, 56.57, 53.37, 38.11, 22.00 (lit.[29] ^{1}H, ^{13}C NMR).

Zirconium L-DIPT enantioselective epoxidation: 2-(2-Methyloxiran-2-yl)ethan-1-ol (2)

L-DIPT (0.148 g, 0.63 mmol) was added to a RBF along with a stir bar and dissolved in chlorobenzene (8 mL). Activated 4Å MS (0.125 g) were added, and the vessel was flushed with argon. Zr(t-BuO)$_4$ (0.118 g, 0.31 mmol) was dissolved in chlorobenzene (2 mL) and added dropwise to the tartrate solution and stirred at 25 °C for 1 h. The solution was cooled in a 5 °C ice bath, and 88% cumene hydroperoxide (0.5 mL, 2.90 mmol) was added dropwise. Isoprenol (0.15 mL, 1.48 mmol) was dissolved in chlorobenzene (1 mL) and transferred to the reaction mixture dropwise. The mixture was stirred for 96 h at 5 °C after which the solution was filtered to remove 4Å MS. The filtrate was loaded onto a silica column and eluted with a Hex/EA gradient to give

(*R*)-epoxide **2** as a clear, colorless oil (0.132g, 87% yield, 82% ee determined by (*S*)-Mosher ester derivative). NMR identical to racemic **2**.

Zirconium D-DIPT enantioselective epoxidation: 2-(2-Methyloxiran-2-yl)ethan-1-ol (2)

D-DIPT (300 mg, 1.28 mmol) was added to a RBF along with a stir bar and dissolved in chlorobenzene (5 mL). Activated 4Å MS (300 mg) were added, and the vessel was flushed with argon. $Zr(t\text{-}BuO)_4$ (0.236 g, 0.62 mmol) was dissolved in chlorobenzene (1 mL) and added dropwise to the tartrate solution and stirred at 25 °C for 30 min. The solution was cooled in a 5 °C ice bath, and 88% cumene hydroperoxide (1 mL, 5.8 mmol) was added dropwise. Isoprenol (0.3 mg, 3.4 mmol) was dissolved in chlorobenzene (1 mL) and transferred to the reaction mixture dropwise. The mixture was stirred for 96 h at 5 °C after which the solution was filtered to remove 4Å MS. The filtrate was loaded onto a silica column and eluted with a Hex/EA gradient to give (*R*)-epoxide **2** as a clear, colorless oil (231 mg, 2.3 mmol, 66% yield, 82% ee determined by (*S*)-Mosher ester derivative). NMR identical to racemic **2**.

tert-Butyldimethyl(2-(2-methyloxiran-2-yl)ethoxy)silane (3). To a RBF was added (*R*)-epoxide **2** (390 mg, 3.8 mmol) along with a stir bar and DCM (25 mL) under argon. The flask was charged with imidazole (630 mg, 9.2 mmol), and the solution was cooled in a 5 °C ice bath. In a separate vial, TBSCl (850 mg, 5.7 mmol) was added and dissolved in DCM (10 mL), and the solution was added dropwise to the epoxide solution. The solution was warmed to 25 °C and was stirred for 24 h. Saturated aqueous NH_4Cl (15 mL) was added, and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 10 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was loaded onto a silica column and purified with a Hex/EA gradient to produce protected (*R*)-epoxide **3** as a clear, colorless oil (0.758 mg, 92% yield). R_f = 0.4 (Hex/EA 9:1) $KMnO_4$ stain. **^{1}H NMR** (400

MHz, $CDCl_3$) δ 3.66 (m, 2H), 2.62 (d, 1H, J = 4.9 Hz), 2.50 (d, 1H, J = 4.9 Hz), 1.78 (m, 1H), 1.62 (m, 1H), 1.28 (s, 3H)), 0.82 (s, 9H), -0.01 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 59.79, 55.57, 54.17, 39.88, 26.00, 21.66, 18.29, -5.28, -5.30. (lit.[37] ^{1}H, ^{13}C NMR).

(*R*,*R*)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediimine chromium(III) azide ((*R*)-4). To a RBF was added chloride (*R*,*R*)-Jacobsen's chromium catalyst (300 mg, 0.47 mmol) along with a stir bar and dry ACN (50 mL). The vessel was then flushed with argon. $AgClO_4$ (119 mg, 0.57 mmol) was added to a separate flask and dissolved with dry ACN (25 mL) then transferred to a dropping funnel. The silver solution was added dropwise to the chromium solution resulting in the precipitation of silver chloride. The solution was stirred for 18 h at 25 °C. The precipitate was filtered and the filtrate was transferred to a RBF along with a stir bar and charged with argon. NaN_3 (100 mg, 1.53 mmol) was added and the solution was stirred at 25 °C for 18 h. To the solution was added diethyl ether (100 mL) and the mixture was transferred to a separatory funnel and washed with brine (3 x 100 mL). The organic layer was dried with $MgSO_4$, filtered, and solvent removed under reduced pressure to give (*R*)-**4** as a dark brown powder (270 mg, 89% yield). IR (solid powder) v 2949, 2904, 2864, 2087, 2055, 1617, 1530, 1459, 1433, 1407, 1385, 1359, 1318, 1269, 1253, 1233, 1198, 1166, 1120, 1098, 1070, 1026, 984, 967, 926, 914, 870, 835, 812, 783, 746, 725, 665, 637, 620 cm^{-1}. (lit. IR[36]).

Jacobsen (*R*)-Epoxide Resolution. An enantiomeric mixture of epoxide **3** (176 mg, 0.81 mmol, 82% ee (*R*)-stereoisomer) was added to a RBF and dissolved in tert-butyl methyl ether (400 µL, 3.4 mmol). A stir bar was added, and the vessel was flushed with argon. The flask was then charged with chromium catalyst (*R*)-**4** (10 mg, 0.016 mmol) and stirred at 25 °C for 5 min. The vessel was cooled in a 5 °C ice bath for 5 min, isopropyl alcohol (30 µL, 0.39 mmol) was added followed by $TMSN_3$ (15 µl, 0.12 mmol), and the mixture was stirred at 25 °C for 2 h. The crude mixture was

transferred to a silica column and purified using a Hex/EA gradient to give enriched (*R*)-epoxide **3** as a clear, colorless oil (148 mg, 84% yield, ≥99% ee determined as the (*S*)-Mosher ester derivative).

1-Azido-4-((tert-butyldimethylsilyl)oxy)-2-methylbutan-2-ol (5). Isolated as a clear, colorless oil (15 mg, 7% yield). R_f = 0.3 (Hex/EA 9:1) $KMnO_4$ stain. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.58 (m, 2H), 3.27 (d, 1H, *J* = 12.2 Hz), 3.22 (d, 1H, *J* = 12.2 Hz), 1.85 (m, 1H), 1.65 (m, 1H), 1.25 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 73.50, 60.74, 60.63, 39.11, 26.00, 25.32, 18.23, -5.41, -5.44. HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{25}N_3NaO_2Si$. 282.1608; Found 282.1590.

(*S*,*S*)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediimine chromium(III) azide ((*S*)-4). To a RBF was added (*S*,*S*)-Jacobsen's ligand (250 mg, 0.45 mmol), a stir bar, dry THF (20 mL), and argon. $CrCl_2$ (78 mg, 0.5 mmol) was added and the mixture was stirred for 24 h at 25 °C. The mixture was concentrated at reduced pressure, dissolved in ether (20 mL), and transferred to a separatory funnel. The organic layer was washed with brine (3 x 50 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in dry ACN (20 mL) and a stir bar was added along with argon. $AgClO_4$ (120 mg, 0.57 mmol) was added to a separate flask and dissolved in dry ACN (25 mL), then transferred to a dropping funnel. The $AgClO_4$ solution was added dropwise to the chromium solution resulting in the precipitation of silver chloride. The solution was stirred for 18 h at 25 °C. The precipitate was filtered and the filtrate was transferred to a RBF along with a stir bar and charged with argon. NaN_3 (101 mg, 1.5 mmol) was added and the solution was stirred at 25 °C for 18 h. To the solution was added diethyl ether (50 mL) and the mixture was washed with brine (3 x 50 mL). The organic layer was dried with

$MgSO_4$, filtered, and solvent removed under reduced pressure to give (*S*)-**4** as a dark brown powder (269 mg, 0.42 mmol, 92% yield). IR identical to catalyst (*R*)-**4**.

Jacobsen (*S*)-Epoxide Resolution:

An enantiomeric mixture of epoxide **3** (305 mg, 1.4 mmol, 82% ee (*S*)-stereoisomer) was added to a RBF and dissolved in tert-butyl methyl ether (700 µL, 5.8 mmol). A stir bar was added, and the vessel was flushed with argon. The flask was then charged with chromium catalyst (*S*)-**4** (18 mg, 0.028 mmol) and stirred at 25 °C for 5 min. The vessel was cooled in a 5 °C ice bath for 5 min, isopropyl alcohol (52 µL, 0.67 mmol) was added followed by $TMSN_3$ (26 µl, 0.21 mmol), and the mixture was stirred at 25 °C for 2 h. The crude mixture was transferred to a silica column and purified using a Hex/EA gradient to give enriched (*S*)-epoxide **3** as a clear, colorless oil (249 mg, 1.15 mmol, 82% yield, ≥99% ee determined as (*S*)-Mosher ester derivative).

Deprotection of TBS protected epoxide 3 to epoxide 2:

In a RBF was added TBS epoxide **3** (148 mg, 0.68 mmol) along with a stir bar, and the flask was flushed with argon. The vessel was cooled in a 5 °C ice bath, and 1M TBAF in THF (820 µL, 0.82 mmol) was added. The solution was stirred at 5 °C for 1 h, and the solvent was removed under reduced pressure. The residue was loaded onto a silica column and purified with a gradient of Hex/EA to give epoxide **2** as a clear oil (64 mg, 91% yield). NMR identical to **2** from epoxidation.

3,5-Dihydroxy-3-methylpentanenitrile (6). To a RBF was added epoxide **2** (170 mg, 1.6 mmol) followed by H_2O (2 mL) and a stir bar. In a separate vial was added NaCN (150 mg, 3.0 mmol) and H_2O (3 mL). Both vessels were cooled in a 5 °C ice bath for 5 min, and then the cyanide solution was added dropwise to the epoxide solution and stirred at 25 °C for 5 h. H_2O (10 mL) and EA (20 mL) were added, and the solution was transferred to a separatory funnel. The organic layer was washed with brine (2 x 20 mL) and dried with $MgSO_4$, filtered, and concentrated under

reduced pressure. The residue was loaded onto a silica column and purified with a Hex/EA gradient to give nitrile **6** as a clear oil (81 mg, 0.63 mmol, 39% yield). R_f = 0.4 (100% EA) $KMnO_4$ stain. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.37 (br, 1H), 4.01 (m, 2H), 3.38 (br, 1H), 2.70 (m, 2H), 2.02, (m, 1H), 1.96 (m, 1H), 1.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 118.08, 71.76, 59.33, 41.02, 31.58, 27.15. (lit.[10] ^{1}H, ^{13}C NMR).

Mevalonic acid (1). Epoxide **2** (1.5 g, 14.6 mmol) was added to a RBF containing a stir bar and cooled in a 5 °C ice bath. A separate flask was charged with sodium cyanide (0.79 g, 16.1 mmol), which was dissolved in H_2O (2 mL) and cooled in a 5 °C ice bath. The cyanide solution was then added to the epoxide flask dropwise slowly over the course of 10 min while maintaining a cold temperature of the reaction mixture. Upon complete addition, the ice bath was removed, and the mixture was stirred at 25 °C for 16 h. The solution was diluted with H_2O (25 mL) and washed with DCM (2 x 20 mL) in a separatory funnel. The aqueous layer was filtered with a fritted filter to remove suspended white participate and was subjected to reduced pressure for 5 min to remove residual DCM.

This solution was transferred to a RBF containing a stir bar, the pH of the solution was increased to pH 12.5 by addition of 1M aqueous NaOH, and the mixture was cooled in a 5 °C ice bath for 10 min. 30% H_2O_2 (20 mL, 176.5 mmol) was added dropwise, and the mixture was stirred at 25 °C for 16 hr. After this period, the mixture was transferred to a separatory funnel and washed with DCM (2 x 30 mL). The aqueous layer was subjected to reduced pressure for 5 min to remove residual DCM, and the solution was transferred to a RBF containing a stir bar. This solution was cooled in a 5 °C ice bath for 10 min, and the pH was lowered to pH 5.6 by dropwise addition of 1M aqueous HCl while taking care to maintain steady bubble formation. The solution was stirred

at 25 °C for 16 h. After this period, the pH of the solution was increased to pH 8.5 by addition of 1M aqueous NaOH, and the solution was stirred for an additional 16 h at 25 °C.

The water was removed under reduced pressure in a 40 °C water bath. The clear viscous/solid residue was dissolved in EtOH (20 mL) added dropwise while stirring vigorously over 10 min. The white NaCl precipitate was filtered, and the solvent was removed under reduced pressure. The residue was again dissolved in EtOH (20 mL) and filtered to remove remaining NaCl, and the solvent was removed under reduced pressure. Residual EtOH was removed by addition of H_2O (5 mL) to the product residue, and solvent was removed under reduced pressure in a 40 °C water bath. The resulting product residue **1** was a clear, colorless syrup containing residual water which required no further purification (2.35 g, 12.2 mmol determined by dimethyl sulfone internal standard, 83% yield). NMR as sodium mevalonate: **^{1}H NMR** (400 MHz, D_2O) δ 3.58 (t, 2H, J = 7.4 Hz), 2.21 (d, 2H, J = 2.9 Hz), 1.68 (t, 2H, J = 7.4 Hz), 1.11 (s, 3H). **^{13}C NMR** (100 MHz, D_2O) δ 180.61, 71.10, 58.15, 48.18, 42.86, 26.30. (lit.[38] ^{1}H NMR). NMR as mevalonic acid – sodium mevalonate syrup (30 mg, 0.16 mmol) dissolved in 500 mM 2.1 pH phosphate D_2O buffer: **^{1}H NMR** (400 MHz, D_2O) δ 3.66 (t, 2H, J = 7.3 Hz), 2.50 (d, 2H, J = 3.1 Hz), 1.80 (t, 2H, J = 7.2 Hz), 1.23 (s, 3H). **^{13}C NMR** (100 MHz, D_2O) δ 175.36, 70.72, 57.51, 45.65, 42.33, 25.75.

ASSOCIATED CONTENT

Supporting Information. Spectra for characterization of all compounds discussed and ^{13}C NMR spectra for % ee determinations are available free of charge at https://pubs.acs.org

Data availability Statement The data underlying this study are available in the published article and its Supporting Information.

AUTHOR INFORMATION

Corresponding Authors

Olaf Wiest, Department of Chemistry and Biochemistry, University of Notre Dame, IN 46556, USA, email: owiest@nd.edu

Paul Helquist Department of Chemistry and Biochemistry, University of Notre Dame, IN 46556, USA, email: phelquis@nd.edu

Authors

Ryan J. OConnell, Department of Chemistry and Biochemistry, University of Notre Dame, IN 46556

Nicholas Dolphin, Department of Chemistry and Biochemistry, University of Notre Dame, IN 46556

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES

1. Haines, B. E.; Wiest, O.; Stauffacher, C. V. The Increasingly Complex Mechanism of HMG-CoA Reductase. *Acc. Chem. Res.* **2013**, *4*, 2416-2426.

2. Berthelot, K.; Estevez, Y.; Deffieux, A.; Peruch, F. Isopentenyl diphosphate isomerase: A checkpoint to isoprenoid biosynthesis. *Biochimie* **2012**, *94*, 1621-1634.

3. Buhaescu, I.; Izzedine, H. Mevalonate pathway: A review of clinical and therapeutical implications. *Clin. Biochem.* **2007**, *40*, 575-584.

4. Choi, E. H. Aging of the skin barrier. *Clin. Dermatol.* **2019**, *37*, 336-345.

5. Katoh, N. Future perspectives in the treatment of atopic dermatitis. *J. Dermatol.* **2009**, *36*, 367-376.

6. Haines, B. E.; Steussy, C. N.; Stauffacher, C. V.; Wiest, O. Molecular modeling of the reaction pathway and hydride transfer reactions of HMG-CoA reductase. *Biochemistry* **2012**, *51*, 7983-7995.

7. Patel, H. N.; Haines, B. E.; Stauffacher, C. V.; Helquist, P.; Wiest, O. Computational Study of Base-Catalyzed Thiohemiacetal Decomposition in Pseudomonas mevalonii HMG-CoA Reductase. *J. Phys. Chem. B.* **2023**, *127*, 4931–4938.

8. Purohit, V.; Steussy, C. N.; Rosales, A. R.; Crtichelows, C. J.; Schmidt, T.; Helquist, P.; Wiest, O.; Mesecar, A.; Cohen, A. E.; Stauffacher, C. V. pH-dependent reaction triggering in PmHMGR crystals for time-resolved crystallography. *Biophys. J.* **2024**, *123*, 622–637.

9. Orru, R. V. A.; Osprian, I.; Kroutil, W.; Faber, K. An efficient large-scale synthesis of (*R*)-(-)-mevalonolactone using simple biological and chemical catalysts. *Synthesis* **1998**, 1259-1263.

10. Lakner, F. J.; Hager, L. P. Chloroperoxidase as enantioselective epoxidation catalyst: An efficient synthesis of (*R*)-(-)-mevalonolactone. *J. Org. Chem.* **1996**, *61*, 3923-3925.

11. Wilson, W. K.; Baca, S. B.; Barber, Y. J.; Scallen, T. J.; Morrow, C. J. Enantioselective Hydrolysis of 3-Hydroxy-3-methylalkanoic Acid Esters with Pig Liver Esterase. *J. Org. Chem.* **1983**, *48*, 3960-3966.

12. Zhang, J.; Yuan, Y.; Wang, Z.; Chen, T. Metabolic engineering of Halomonas bluephagenesis for high-level mevalonate production from glucose and acetate mixture. *Metabol. Eng.* **2023**, *79*, 203-213.

13. Shimizu, M.; Kamikubo, T.; Ogasawara, K. A new enantiocontrolled synthesis of (-)-(*R*)-mevalonolactone. *Tetrahedron Asym.* **1997**, *8*, 2519-2521.

14. Davis, F. A.; Reddy, G. V.; Chen, B. C.; Anil, K.; Haque, M. S. Enantioselective Synthesis of 2-Methyl-2-hydroxy-γ-butyrolactone and Its Application in the Asymmetric Synthesis of Frontalin and Mevalonolactone. *J. Org. Chem.* **1995**, *60*, 6148-6153.

15. Ferraboschi, P.; Canevotti, R.; Grisenti, P.; Santaniello, E. A new flexible synthesis of (*R*,*S*)-mevalonolactone. *J. Chem. Soc, Perkin 1* **1987**, 2301-2303.

16. Kawakami, Y.; Hiratake, J.; Yamamoto, Y.; Oda, J. I. An asymmetric synthesis of 2,4-dimethylvalerolactone and mevalonolactone using chiral binaphthyldiamine derivatives. *Chem. Comm.* **1984**, 779-781.

17. Cornforth, R. H.; Cornforth, J. W.; Popják, G. Preparation of *R*- and *S*-mevalonolactones. *Tetrahedron* **1962**, *18*, 1351-1354.

18. Hoffman, C. H.; Wagner, A. F.; Wilson, A. N.; Walton, E.; Shunk, C. H.; Wolf, D. E.; Holly, F. W.; Folkers, K. Synthesis of DL-3,5-Dihydroxy-3-methylpentanoic Acid (Mevalonic Acid). *J. Am. Chem. Soc.* **1957**, *79*, 2316-2318.

19. Katsuki, T.; Sharpless, K. B. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

20. Bolitt, V.; Mioskowski, C.; Bhatt, R. K.; Falck, J. R. Synthesis of (*S*)-(+)-Mevalonolactone and Mevalonate Analogues. *J. Org. Chem.* **1991**, *56*, 4238-4240.

21. Ray, N. C.; Raveendranath, P. C.; Spencer, T. A. A Synthesis of (*R*)-Mevalonolactone. *Tetrahedron* **1992**, *48*, 9427-9432.

22. Ohta, T.; Tabei, N.; Nozoe, S. Synthesis of (*R*)-(-)- and (2*R*, 3*R*)-(-)-[2-2H]mevalonolactones. *Heterocycles* **1989**, *28*, 425-432.

23. Schneider, J. A.; Yoshihara, K. Facile and Highly Effective Synthesis of (-)-Mevalonic-2-d and -4-d Acid Lactones. *J. Org. Chem.* **1986**, *51*, 1077-1079.

24. Hanson, J. R. Fifty years of the synthesis of labelled mevalonic acid. *J. Chem. Res.* **2008**, 241-247.

25. Dickschat, J. S.; Citron, C. A.; Brock, N. L.; Riclea, R.; Kuhz, H. Synthesis of deuterated mevalonolactone isotopomers. *Europ. J. Org. Chem.* **2011**, 3339-3346.

26. Lewer, P.; Macmillan, J. Reinvestigation of a synthesis of (*R*, *S*)-mevalonolactone. *J. Chem. Soc, Perkin 1* **1983**, 1417-1420.

27. Eguchi, T.; Watanabe, E.; Kakinuma, K. Practical enantioselective synthesis of fully deuterated (*R*)-mevalonolactone. *Tetrahedron* **2003**, *59*, 6035-6038.

28. Li, Z.; Yamamoto, H. Zirconium(IV)- and hafnium(IV)-catalyzed highly enantioselective epoxidation of homoallylic and bishomoallylic alcohols. *J. Am. Chem. Soc.* **2010**, *132*, 7878-7880.

29. Okachi, T.; Murai, N.; Onaka, M. Catalytic enantioselective epoxidation of homoallylic alcohols by chiral zirconium complexes. *Org. Lett.* **2003**, *5*, 85-87.

30. Neises, B.; Steglich, W. Simple Method for the Esterification of Carboxylic Acids. *Angew. Chem. Intl. Ed.* **1978**, *17*, 522-524.

31. Dale, J. A.; Dull, D. L.; Mosher, H. S. α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines. *J. Org. Chem.* **1969**, *34*, 2543-2549.

32. Lebel, H.; Jacobsen, E. N. Chromium catalyzed kinetic resolution of 2,2-disubstituted epoxides. *Tetrahedron Lett.* **1999**, *40*, 7303-7306.

33. Navrátilová, H. Enantiomeric analysis of (3*S*, 4*R*)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine by 19F NMR spectroscopy. *Mag. Res. Chem.* **2001**, *39*, 727-730.

34. Hansen, T.; Vermeeren, P.; Haim, A.; van Dorp, M. J. H.; Codée, J. D. C.; Bickelhaupt, F. M.; Hamlin, T. A. Regioselectivity of Epoxide Ring-Openings via SN2 Reactions Under Basic and Acidic Conditions. *Europ. J. Org. Chem.* **2020**, *2020*, 29826-29858.

35. Lister, M. W. Some Observations on Cyanic Acid and Cyanates. *Can. J. Chem.* **1955**, *33*, 426–440.

36. Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. On the Mechanism of Asymmetric Nucleophilic Ring-Opening of Epoxides Catalyzed by (Salen) Cr(III) Complexes. *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925.

37. Hubbell, A. K.; Lapointe, A. M.; Lamb, J. R.; Coates, G. W. Regioselective Carbonylation of 2,2-Disubstituted Epoxides: An Alternative Route to Ketone-Based Aldol Products. *J. Am. Chem. Soc.* **2019**, *141*, 2474–2480.

38. Wong, B. J.; Gerlt, J. A. Evolution of Function in the Crotonase Superfamily: (3*S*)-Methylglutaconyl-CoA Hydratase from Pseudomonas Putida. *Biochemistry* **2004**, *43*, 4646–4654.