6488-88-6; 29, 26559-04-6; 31, 116830-73-0; 32, 116830-74-1; 33, 133797-83-8; 34, 116882-69-0; 35, 133797-84-9; 36, 133797-85-0; *N*-methylimidazole, 616-47-7; *N*-methylpyrazole, 930-36-9; phenyl vinyl sulfoxide, 20451-53-0.

Supplementary Material Available: ^{13}C NMR of compound 34, individual assignments using SFORD, SEFT, and HETNOE techniques (Figure 1), percentage heteronuclear NOE enhancements on irradiation of some protons of compound 34 in $CDCl_3$ (Table II), and elemental analyses of new compounds (Table IV) (3 pages). Ordering information is given on any current masthead page.

Synthesis of (*S*)-(+)-Mevalonolactone and Mevalonate Analogues[1]

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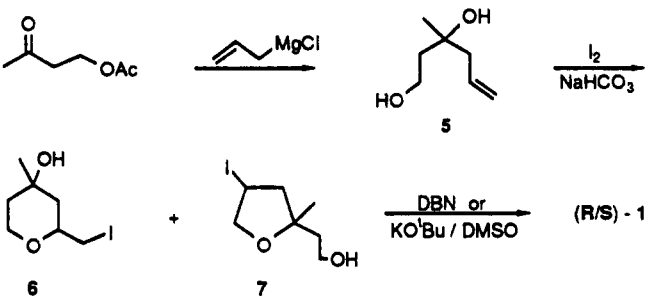
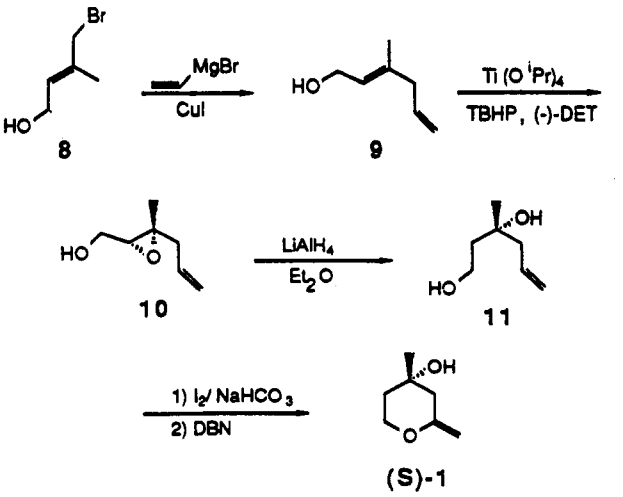
Tetrahydropyran (*R/S*)-1, a vinylidene analogue of mevalonolactone, was prepared by addition of excess allyl Grignard to 4-acetoxy-2-butanone, iodoetherification of the resultant diol 5, and DBN-mediated dehydrohalogenation. Sharpless asymmetric epoxidation of 3-methylhexa-2,5-dien-1-ol (9) gave epoxide 10 that was reduced to diol 11 (>95% ee) by $LiAlH_4$. Annulation and elimination of HI as described for 5 furnished (*S*)-1. Ozonolysis of (*S*)-1 yielded (*S*)-mevalonolactone (2), whereas bromomethoxylation and controlled hydrolysis led to 3, a reactive analogue of (*S*)-mevalonic acid. Analogue 4, a nonionizable lipophilic version of (*S*)-mevalonic acid, was generated upon exposure of (*S*)-1 or 2 to excess Tebbe–Grubbs reagent.

Living systems precisely regulate the biosynthesis of mevalonate (present as mevalonolactone or mevalonic acid), the essential precursor to a vast array of terpenoids, sterols, cytokines, and other isoprenoids.[2] Issues concerning the mechanism of regulation[3] and the disposition of mevalonate between competing pathways[4] have come under greater scrutiny recently with the ultimate aim of intervening in vital cellular functions ranging from cholesterol homeostasis[5] to cell proliferation promoted by prenylated enzymes such as *ras*-protein.[6] While several syntheses of mevalonolactone have been reported,[7] little is known about the pharmacologic profile[8] of the unnatural *S* enantiomer 2 and its interactions with regulatory components of the mevalonate and isoprenoid pathways. To expedite current biological evaluations of structural variance, we describe herein an efficient total synthesis of the vinylidene analogue 1 of (*S*)-mevalonolactone and its

Scheme I



Scheme II



further transformation to 2 as well as the seco analogues 3 and 4.

Convenient access to (*R/S*)-1 on a multigram scale was achieved by addition of allylmagnesium chloride to 4-

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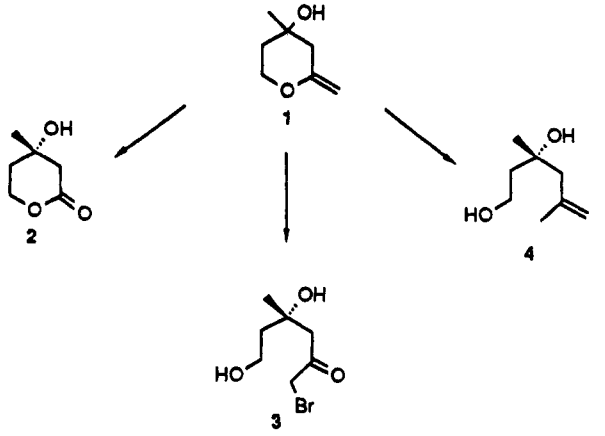
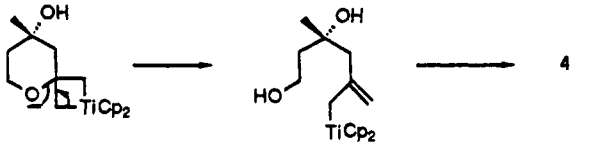


acetoxy-2-butanone[9] (Scheme I). Intramolecular iodoetherification[10] of the resultant diol 5 gave cyclic iodide 6 as a single diastereomer (^1H and ^{13}C NMR) accompanied by a small amount (10%) of the chromatographically separable tetrahydrofuran 7. DBN- or KO-*t*-Bu-mediated dehydrohalogenation of 6 at room temperature smoothly generated (*R*/*S*)-1 in 20% overall yield.

To obtain (*S*)-1 (Scheme II), bromo alcohol 8, prepared[11] in two steps from isoprene, was coupled with vinylmagnesium bromide via copper catalysis[12] to furnish dienol 9 (60%). The epoxide 10 derived from 9 by Sharpless asymmetric epoxidation[13] (98%) was reduced regiospecifically[14] to diol 11 (80%) using $LiAlH_4$. The enantiomeric purity of 11 (>95% ee) was determined by ^1H NMR analysis utilizing a chiral shift reagent. Annulation and elimination of HI as described for 6 produced (*S*)-1 (70%).

As anticipitated, (*S*)-1 proved to be a versatile precursor for other mevalonates. Its low-temperature ozonolysis in $MeOH/CH_2Cl_2$ followed by Me_2S workup gave rise to (*S*)-mevalonolactone 2; 84%, chromatographically and spectrally identical with a racemic standard (Aldrich Chemical Co.). Bromomethoxylation of (*S*)-1 with *N*-bromosuccinimide (NBS) in CH_2Cl_2/MeOH at −40 °C gave the corresponding methyl bromo acetal as an ~1:1.1 mixture of diastereomers. Mild acidic hydrolysis of the latter and flash chromatographic purification afforded α-bromo ketone 3 (73% from (*S*)-1), a potentially reactive analogue of (*S*)-mevalonic acid.

It was also of interest to prepare analogue 4, a nonionizable lipophilic version of (*S*)-mevalonic acid in which the carboxyl has been replaced by a 2-propene unit. This was achieved in a single step from (*S*)-1 by exposure to the Tebbe–Grubbs reagent[15] in THF/CH_2Cl_2. Yields of 4 improved proportionately with increasing amounts of reagent to a maximum of 45–50% using 3 equiv and decreased thereafter. Likewise, 2 evolved 4 under identical conditions and in similar yield. This intriguing transformation can be envisioned as a metathesis of the enolic olefin in 1 (or generated in situ from 2) via a titanocyclobutane, possibly assisted by complexation with the C-3 tertiary alcohol, leading to a homologated allylic titanate that yields 4 upon hydrolytic isolation (eq 1). The structure of 4 was confirmed by spectral and chromatographic comparisons with a racemic standard prepared by addition of excess (2-methyl-2-propenyl)magnesium bromide to 4-acetoxy-2-butanone.



Experimental Section

General. NMR spectra were recorded on a Bruker WP-200 or AC-250 and are reported in ppm relative to tetramethylsilane (δ). Melting points are uncorrected. Optical rotations were obtained using a Jobin-Yvon Digital 71 or Perkin-Elmer 241 MC polarimeter. All reactions were maintained under an argon or nitrogen atmosphere. Anhydrous solvents were freshly distilled from sodium benzophenone ketyl except for CH_2Cl_2, which was distilled from P_2O_5 or CaH_2. Analytical TLC used Merck silica gel 60 F-254 plates, and column chromatography was performed using Merck silica gel 60 (230–400 mesh).

(*R*/*S*)-3-Methyl-5-hexene-1,3-diol (5). An ethereal solution (10 mL) of 4-acetoxy-2-butanone[9] (598 mg, 4.6 mmol) was added dropwise to a room temperature solution of allylmagnesium chloride (18.4 mmol, 4 equiv) in Et_2O (20 mL). After the solution was heated at reflux for 20 h, excess reagent was quenched with H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Chromatographic purification over SiO_2 (Et_2O, $R_f \approx 0.45$) afforded 5 (359 mg, 60%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28 (s, 3 H), 1.72 (t, J = 6 Hz, 2 H), 2.27 (d, J = 12 Hz, 2 H), 2.82 (br s, 2 × OH), 3.87 (t, J = 6 Hz, 2 H), 5.18 (m, 2 H), 5.88 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.67, 41.48, 47.01, 59.70, 73.22, 118.95, 133.61. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.50; H, 10.70.

2-(Iodomethyl)-4-hydroxy-4-methyltetrahydropyran (6). To a 0 °C solution of 5 (260 mg, 2 mmol) in a 1:1 biphasic mixture of CH_2Cl_2/4% aqueous $NaHCO_3$ was added a CH_2Cl_2 (40 mL) solution of I_2 (1.01 g, 4 mmol) over 45 min. After 10 h at ambient temperature, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with 37% aqueous $NaHSO_3$ and brine, dried over Na_2SO_4, and concentrated. Chromatographic purification over silica gel (Et_2O/hexane (4:1), $R_f \approx 0.51$) furnished 6 (70%): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.31 (s, 3 H), 1.35 (dd, J = 12.5, 14 Hz, 1 H), 1.45 (dd, J = 12.5, 9 Hz, 1 H), 1.70 (m, 3 H), 3.09 (dd, J = 8.7, 10.8 Hz, 1 H), 3.17 (dd, J = 6.1, 10.8 Hz, 1 H), 3.62 (dddd, J = 14, 9, 8.7, 6.1 Hz, 1 H), 3.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.15, 31.47, 38.04, 44.20, 63.62, 67.75, 72.02. Anal. Calcd for $C_7H_{13}IO_2$: C, 32.83; H, 5.12. Found: C, 32.78; H, 5.01.

Analogue (*R*/*S*)-1. An admixture of 6 (330 mg, 1.28 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (800 mg, 6.44 mmol) was stirred at room temperature for 10 h. The mixture was diluted with CH_2Cl_2/Et_3N (40 mL, 95:5) and rapidly passed through a column of silica gel. The column was washed with the same solvent (50 mL), and the combined organic solutions were evaporated under reduced pressure to give (*R*/*S*)-1 as a colorless oil in nearly quantitative yield: TLC (SiO_2) Et_2O, $R_f \approx 0.42$; ^1H NMR (C_6D_6, 250 MHz) δ 0.92 (s, 3 H), 1.21–1.29 (m, 2 H), 1.97 (ddd, J = 0.9, 1.9, 13.9 Hz, 2 H), 3.61 (dt, J = 4.8, 12.7 Hz, 1 H), 3.79–3.89 (m, 1 H), 4.08 (dd, J = 1, 1.9 Hz, 1 H), 4.67 (d, J = 0.9 Hz, 1 H); ^{13}C NMR (C_6D_6, 62.5 MHz) δ 28.71, 38.33, 43.88, 65.46, 67.80, 93.69, 158.58; PICI (CH_4) MS *m*/*e* (relative intensity) 129 (M + 1, 23), 111 (100), 71 (50), 69 (33). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.81; H, 9.30. To minimize decomposition, 1 is best stored cold in pentane over anhydrous K_2CO_3 or neat with a small amount of Et_3N.

Alternatively, a solution of 6 (256 mg, 1 mmol) in DMSO (2 mL) was added dropwise to a room temperature solution of KO-*t*-Bu (123 mg, 1.1 mmol) in DMSO (8 mL). After 3 h, the mixture was poured into H_2O (25 mL) and extracted with Et_2O

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(4 × 15 mL). The combined ethereal extracts were washed with H_2O (3 × 10 mL) and brine (10 mL), dried over K_2CO_3, and concentrated under reduced pressure. Passage of the residue over a short SiO_2 column using Et_2O/hexane (4:1) containing 1.5% Et_3N furnished (*R*/*S*)-1 (114 mg, 89%).

3-Methyl-2(*E*),5-hexadien-1-ol (9). To a −50 °C solution of freshly prepared vinylmagnesium bromide (0.15 mol) in anhydrous THF (150 mL) was added CuI[12] (2.88 g, 15 mmol). After 30 min, bromo alcohol 8[11] (10 g, 0.06 mol) in anhydrous THF (10 mL) was slowly added. The mixture was allowed to warm to room temperature over 10 h then quenched with saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Chromatographic purification of the residue over silica gel (Et_2O/hexane (1:1), $R_f \approx 0.50$) gave 9[16] (60%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.70 (s, 3 H), 2.77 (d, J = 10 Hz, 2 H), 4.17 (d, J = 10 Hz, 2 H), 5.00–5.10 (m, 2 H), 5.45 (t, J = 10 Hz, 1 H), 5.78–5.81 (m, 1 H); IR ($CHCl_3$) 3600, 1640 cm^{-1}. Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.87; H, 10.69.

3-Methyl-2(*R*),3(*R*)-epoxy-5-hexen-1-ol (10). *tert*-Butyl hydroperoxide (15 mL of a 3 M solution in toluene, 45 mmol) was added dropwise to a well-stirred, −40 °C solution of Ti(*i*-PrO)$_4$ (6.39 g, 22.5 mmol), diethyl (−)-tartrate (4.86 g, 23.6 mmol), and dienol 9 (2.54 g, 22.5 mmol) in 200 mL of dry CH_2Cl_2. After 20 h at −30 °C, the reaction was quenched with 10% aqueous tartaric acid solution. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Chromatographic purification of the residue over SiO_2 (Et_2O/hexane (4:1), $R_f \approx 0.35$) afforded 10 (98%): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 3 H), 1.72 (s, 1 H), 2.32–2.34 (m, 2 H), 3.02–3.05 (m, 1 H), 3.76–3.79 (m, 2 H), 5.10–5.18 (m, 2 H), 5.19–6.03 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.88, 42.75, 60.64, 61.36, 62.10, 118.34, 132.88; $[\alpha]^{22}_D$ +7° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.41; H, 9.62.

(*R*)-3-Methyl-5-hexene-1,3-diol (11). Epoxide 10 (5.76g, 45 mmol) in dry Et_2O (60 mL) was added dropwise to a 0 °C suspension of $LiAlH_4$ (1.7g, 45 mmol) in Et_2O (100 mL). After 30 min, the ice bath was removed and the mixture stirred for 10 h. Excess hydride was destroyed by successive addition of H_2O and NaOH solution[17] and filtration over Celite to remove the aluminate salts. After generously washing the filter cake with CH_2Cl_2, the combined organic solutions were concentrated and the residue was purified by chromatography over SiO_2(Et_2O, $R_f \approx 0.45$) to give 11 (80%), whose ^1H and ^{13}C spectra were identical with 5: $[\alpha]^{22}_D$ +15° (*c* 1.0, $CHCl_3$) (lit.[7c] $[\alpha]_D$ +5.1° (*c* 1.4, EtOH)). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.38; H, 10.74.

The enantiomeric purity of 11 (>95% ee) was determined by ^1H NMR analysis ($CDCl_3$, 200 MHz) in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) under conditions in which 5 was resolved.

(*S*)-1. Iodoetherification of 11 as described for 5 furnished an (iodomethyl)tetrahydropyran identical with 6: mp 81–82 °C (Et_2O); $[\alpha]^{22}_D$ +20° (*c* 1.0, $CHCl_3$). Subsequent dehydrohalogenation as applied to 6 yielded (*S*)-1 as a colorless oil: $[\alpha]^{22}_D$ +4.8° (*c* 1.2, EtOH). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.86; H, 9.20.

(*S*)-Mevalonolactone (2). A stream of O_3 (~3% in dry O_2) was bubbled through a −78 °C solution of (*S*)-1 (325 mg, 2.54 mmol) in CH_2Cl_2/MeOH ((4:1), 15 mL) until the blue coloration of excess O_3 persisted for 5 min (~30 min). After another 15 min, the system was purged with N_2, excess Me_2S was added, and the mixture allowed to warm to ambient temperature over 12 h. Evaporation of the solvent and chromatography over SiO_2 using EtOAc afforded 2 (277 mg, 84%) as a colorless oil, spectrally and chromatographically identical with an authentic racemic standard (Aldrich Chemical Co.): $[\alpha]^{23}_D$ +22.3° (*c* 1.5, EtOH) (lit.[7a] $[\alpha]^{20}_D$ +21.7° (*c* 0.75, EtOH)). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.51; H, 7.82.

Analogue 3. To a −40 °C solution of NBS (50 mg, 0.28 mmol) in CH_2Cl_2/MeOH (5:1, 2.5 mL) was added dropwise a solution of (*S*)-1 (30 mg, 0.23 mmol) in CH_2Cl_2 (1 mL). After 1 h, the reaction mixture was washed with aqueous 5% $NaHCO_3$ (5 mL), aqueous $Na_2S_2O_3$ (5 mL), and brine (5 mL) and dried over Na_2SO_4. Column chromatography of the residue after solvent evaporation gave 1:1.1 mixture of diastereomeric methyl bromo acetals[18] (48 mg, 87%) as a colorless oil: ^1H NMR (C_6D_6, 250 MHz) δ 1.10 (s, 3 H), 1.15–1.50 (m, 3 H), 2.02–2.05 (m, 1 H), 2.71 and 2.70 (s, diastereomeric methyls, 3 H), 2.55–3.20 (m, 2 H), 3.30–3.70 (m, 2 H), 4.10 (br s, 1 H); TLC (SiO_2) Et_2O, $R_f \approx 0.61$.

To a 0 °C solution of the above methyl bromo acetals (23 mg) in THF/H_2O (4:1, 2.5 mL) was added 0.1 mL of 1 N aqueous HCl. After 12 h, the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (3 × 5 mL). The combined ethereal extracts were washed with H_2O (2 × 5 mL) and brine and dried over Na_2SO_4. Column chromatography over SiO_2 using Et_2O/hexane (4:1) gave 3 (18 mg, 84%) as colorless plates (mp 74–76 °C dec) that exist predominantly as the lactol tautomer: ^1H NMR (C_6D_6, 250 MHz) δ 0.85 (s, 3 H), 1.13–1.35 (m, 3 H), 1.53–1.67 (m, 1 H), 2.70 (br s, 1 H, D_2O exchangeable), 3.09–3.22 (m, 2 H), 3.43–3.49 (m, 1 H), 3.89–3.99 (m, 1 H), 4.40 (br s, 1 H, D_2O exchangeable); ^{13}C NMR (C_6D_6, 62.5 MHz) δ 30.40, 37.36, 40.50, 42.10, 57.24, 68.31, 94.88; PICI (CH_4) MS *m*/*e* (relative intensity) 227 (1), 225 (1), 209 (91), 207 (98), 191 (37), 189 (38), 179 (7), 71 (100); IR (Nujol) 3510, 3300, 1260, 1240, 1210, 1060, 940 cm^{-1}; TLC (SiO_2) Et_2O, $R_f \approx 0.47$; HRMS calcd for $C_7H_{13}BrO_3$ 224.0049, found 224.0035.

Analogue 4. To a −30 °C solution of Tebbe–Grubbs reagent[15] (1.14 g, 4.02 mmol, 3 equiv) in THF/CH_2Cl_2 (5:1, 8 mL) was added 2 (174 mg, 1.34 mmol) in CH_2Cl_2(3 mL) to give a dark red, homogeneous solution. After 2 h, the mixture was warmed to 0 °C and maintained at that temperature for another 1 h then poured into a vigorously stirring solution of 10% aqueous NaOH. Extractive isolation using Et_2O (3 × 10 mL) and column chromatography afforded 4 (89 mg, 46%) as a colorless oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (s, 3 H), 1.62–1.68 (m, 2 H), 1.80 (s, 3 H), 2.17 (d, J = 16 Hz, 1 H), 2.23 (d, J = 16 Hz, 1 H), 3.65–3.80 (m, 2 H), 4.67 (s, 1 H), 4.85 (s, 1 H); PICI (CH_4) MS *m*/*e* (relative intensity) 145 (M + 1, 21), 127 (75); TLC (SiO_2), Et_2O, $R_f \approx 0.43$; $[\alpha]^{22}_D$ +8.1° (*c* 1.4, EtOH). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.86; H, 11.25.

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Supplementary Material Available: ^1H NMR spectrum of 3 (1 page). Ordering information is given on any current masthead page.

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