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A Synthesis of (*R*)-Mevalonolactone

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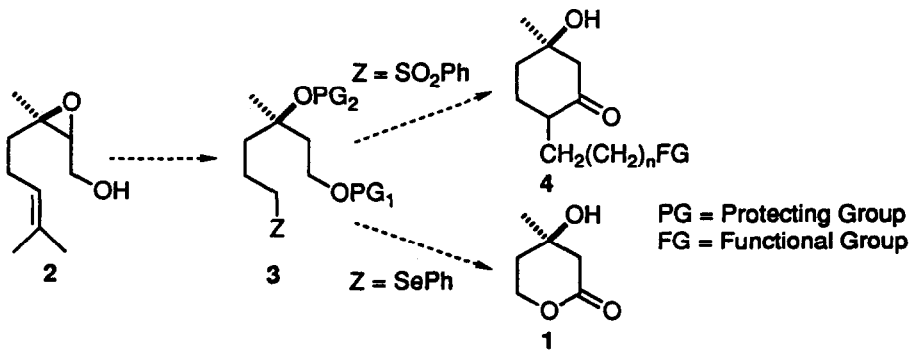
Abstract: *An enantioselective synthesis of (R)-mevalonolactone (1) has been accomplished starting from known epoxide 2, prepared with >95% ee by asymmetric epoxidation of nerol. Functional group manipulation of 2 and ozonolysis afforded intermediate 8, which was converted to 11 via phenylselenoxide formation, followed by appropriate oxidations and deprotection, to afford 1.*

Mevalonic acid, shown in **1** in its cyclized form, mevalonolactone, has a centrally important biochemical role[1], but there is currently available no convenient assay for the measurement of its concentration in biological media. Development of a radioimmunossay to address this deficiency would require synthesis of compounds (haptens), structurally resembling either mevalonic acid or **1**, for attachment to proteins in order to produce suitable antibodies. We have been engaged in the preparation of appropriate cyclohexane derivatives as prospective haptens with the hope that these will serve as adequate approximations of the cyclic structure of **1**, which distinguishes it from many otherwise similar biochemicals. The preparation in this context of the hemisuccinate derivatives of *cis*- and *trans*-1-methylcyclohexane-1,4-diols has previously been described.[2]

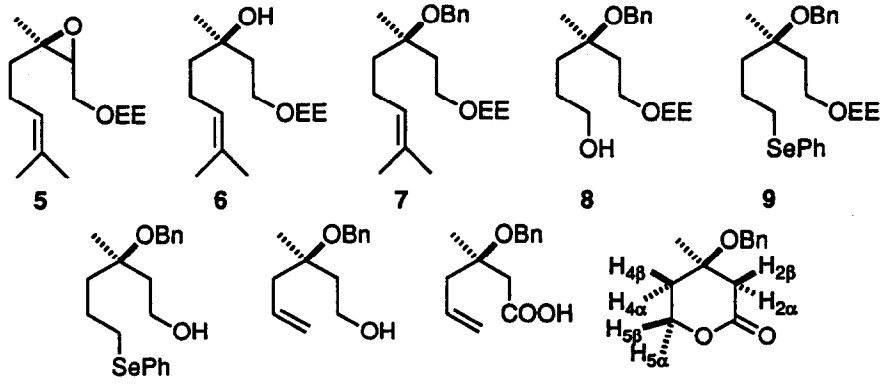
In order to develop the desired antibodies, samples of (*R*)-mevalonolactone (**1**) would also be required for binding assays. A number of syntheses of **1** have been described[3,4,5], but it seemed attractive to us to undertake a synthetic pathway which could lead via a common intermediate to both prospective haptens and **1**. An appealing starting material for such a divergent synthetic strategy was the (2*S*,3*R*)-epoxide **2**, which has been prepared with 94% ee by Sharpless asymmetric epoxidation[6] of the inexpensive nerol. It was envisioned, as illustrated below, that **2** could be converted to **3** (Z = OH), which then could be carried on, either through carbocycle formation to haptens of type **4** or, instead, to (*R*)-mevalonolactone (**1**). This paper describes the details of completion of the latter sequence, synthesis of **1** from **2**. After this work was largely completed, a conceptually similar synthesis of **1** from the (2*S*,3*S*)-epoxide derived from geraniol was reported.[7]



Epoxide **2** was prepared essentially according to the original procedure of Katsuki and Sharpless,[6] except that excess *t*-butylhydroperoxide was removed by Na_2SO_3 reduction,[8] leading to direct isolation of a quantitative yield of **2**, in which none of its enantiomer could be detected by chiral shift reagent analysis,[9] so that the ee presumably is > 95%. The primary hydroxyl group of **2** was protected by formation of ethoxyethyl ether **5** in 95% yield, and reduction of **5** with $LiAlH_4$ afforded 92% of **6**. Conversion of **6** to its benzyl ether **7** was then accomplished in 97% yield, followed by ozonolysis in 99:1 CH_2Cl_2:pyridine[10] and treatment with $LiAlH_4$ to afford 80% of **8** (3, Z = OH). If pyridine was not added to the ozonolysis medium, the tertiary benzyl protecting group was lost in this process, presumably via its oxidation to the benzoate ester.

For conversion to **1**, an additional carbon had to be removed from **8**. This was achieved by conversion to phenylselenide **9**, followed by oxidative elimination to form an alkene[11] which could be cleaved by further oxidation. Transformation of **8** to **9** proved to be the only difficult step in the synthesis of **1**. Among a variety of procedures tried, use of N-(phenylseleno)phthalimide with tri-*n*-butylphosphine[12] proved most successful, affording 87% of **9**, which was, however, tenaciously contaminated with a small amount of diphenyldiselenide. After removal of the ethoxyethyl protecting group from **9** by use of hydrochloric acid-impregnated silica gel,[13] pure phenylseleno alcohol **10** was obtained in only 44% overall yield from **8**.

Completion of the synthesis of **1** proceeded smoothly. Conversion of **10** to alkenol **11** was accomplished in quantitative yield by treatment of **10** with N-(*p*-toluenesulfonyl)phenyloxaziridine[14] in the presence of diisopropylamine,[15] followed by appropriate warming. Oxidation of **11** with pyridinium dichromate in DMF[16] gave 67% of **12**, and reductive ozonolysis of **12** then afforded 71% of benzyl ether **13**, whose ^1H NMR spectrum showed, for its δ-lactone portion, a spin-spin splitting pattern similar to that of **1**, including the pronounced long-range W coupling (J = 2.2 Hz) between the usually equatorial $H_{2\beta}$ and $H_{4\beta}$.[17] Removal of the benzyl group was cleanly effected by catalytic hydrogen transfer with palladium-on-carbon and ammonium formate[18] to afford **1** (88%), which had spectroscopic properties identical with those of a commercial sample of (*R*,*S*)-**1**, and which can be assumed with confidence to have the same ee as the **2** from which it was prepared.



EE = $CH(CH_3)OCH_2CH_3$

Experimental Section

IR spectra were run neat as thin films. ^1H and ^{13}C NMR spectra were recorded at 299.95 and 75.430 MHz, respectively, in $CDCl_3$. In the ^{13}C NMR spectra of compounds containing the ethoxyethyl protecting group, certain carbons appear as two signals owing to diastereoisomerism; such signals are enclosed in parentheses. Low-resolution mass spectra were run at 35 or 70 eV using a solid probe. TLC was conducted on precoated 0.2-mm silica gel 60 plates from EM Science, and the spots were visualized with UV light or *p*-anisaldehyde spray. THF and PhH were distilled from sodium benzophenone ketyl, and Et_2O was distilled from $LiAlH_4$ before use. CH_2Cl_2 was distilled from CaH_2. All reagents were purchased from Aldrich Chemical Co., Milwaukee, WI. Solvents and reagents were used as supplied without further purification unless otherwise stated. All reactions were carried out under an atmosphere of dry argon.

(2*S*,3*R*)-2,3-Epoxy-7-methyl-6-octen-1-ol (2). Exactly according to the procedure of Katsuki and Sharpless,[6] asymmetric epoxidation of 5.0 g (5.7 mL, 0.032 mol) or nerol was conducted to give 6.94 of crude product which was dissolved in 100 mL of CH_2Cl_2, mixed with 50 mL of a freshly-prepared 10% Na_2SO_3 solution,[8] and stirred vigorously for 3 h. The organic layer was separated, washed with 20 mL of brine, dried over $MgSO_4$, and evaporated to give 5.56 g (100%) of **2** as a colorless oil: ^1H NMR δ 1.34 (s, 3H), 1.40-1.70 (m, 2H), 1.62 (s, 3H), 1.69 (s, 3H), 2.03-2.19 (m, 2H), 2.97 (dd, J = 7.0, 4.2 Hz, 1H), 3.66 (m, 1H), 3.81 (m, 1H) 5.09 (m, 1H), essentially identical with lit.[19] ^1H NMR. The % ee in this **2** was determined by use of $Eu(hfc)_3$ as described[9] for linalool, with (*R*,*S*)-**2**, prepared by $VO(acac)_2$ catalyzed *t*-butylhydroperoxide epoxidation of nerol,[8] being used to demonstrate separation of enantiomers. No (*S*)-**2** could be detected, which is taken to indicate ee > 95%.

(6*R*,7*S*)-6,7-Epoxy-2,6,9-trimethyl-8,10-dioxa-2-tridecene (5). According to a procedure of Meyers[20], to 50 mL of freshly-distilled ethyl vinyl ether at 0 °C was added with stirring 0.2 g of *p*-TsOH and 11.2 g (66 mmol) of **2**. The mixture was allowed to warm to rt, stirred for 1 h, diluted with 200 mL of hexane, and filtered through a pad of basic alumina, which was in turn washed with a further 100 mL of hexane. Evaporation of solvent afforded 15.2 g (95%) of **5** sufficiently pure, as judged by TLC, for use in subsequent reactions. Chromatography on basic alumina with 1:1 EtOAc: hexane gave an analytical sample of **5**: IR 2940, 1440, 1375, 1090 cm^{-1}; ^1H NMR δ 1.21 (t, J = 7.1 Hz, 3H), 1.26-1.30 (m, 2H), 1.33 (d, J = 6.0 Hz, 3H), 1.34 (s, 3H), 1.62 (s, 3H), 1.69 (s, 3H), 2.12 (m, 2H), 2.94 (dd, J = 6.4, 4.6 Hz, 1H), 3.4-3.8 (m, 4H), 4.77 (q, J = 5.4 Hz, 1H), 5.10 (bt, J = 6.9 Hz, 1H); ^{13}C NMR δ 15.2 17.5, (19.5, 19.7), 22.0, 24.0, 25.5, (33.1, 33.1), (60.3, 60.5), (60.7, 60.8), (62.4, 62.9), (63.0, 63.3), (99.4, 99.5), 123.4, 132.0. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.51; H, 10.83.

(6*R*)-6-Hydroxy-2,6,9-trimethyl-8,10-dioxa-2-tridecene (6). To a well-stirred slurry of 1.2 g (32 mmol) of $LiAlH_4$ in 250 mL of anhydrous ether at 0 °C was added dropwise a solution of 5.00 g (21 mmol) of **5** in 150 mL of ether. The mixture was stirred for 16 h at rt. Excess $LiAlH_4$ was then decomposed by careful dropwise addition of H_2O. The reaction mixture was filtered and the filtrate was dried over $MgSO_4$ and evaporated to afford 4.64 g (92%) of **6** as a colorless oil which was homogeneous by TLC. Chromatography on basic alumina with 3:7 EtOAc:hexane or distillation at 92-96 °C (0.25 mm Hg) gave **6**: IR 3470, 2920, 1445, 1370, 1340, 1090, 935, 835 cm^{-1}; ^1H NMR δ 1.22 (s, 3H), 1.22 (t, J = 6.6 Hz, 3H), 1.32 (d, J = 5.7 Hz, 3H), 1.51 (m, 2H), 1.62 (s, 3H), 1.69 (s, 3H), 1.86 (m, 2H), 2.05 (m, 2H), 3.01 (bs, 1H), 3.50 (m, 1H), 3.66 (m, 2H), 3.85 (m, 1H), 4.70 (q, J = 5.7 Hz, 1H), 5.12 (m, 1H). ^{13}C NMR δ 15.3, 17.6, 19.7, 22.7,

25.7, (26.5, 26.6), 39.8, (42.2, 42.3), 61.0, 62.0, 72.2, (99.7, 99.7), 124.5, 131.5. Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.97; H, 11.48.

(6*R*)-2,6,9-Trimethyl-6-benzyloxy-8,10-dioxa-2-tridecene (7). To a suspension of 2.29 g (57 mmol) of oil-free potassium hydride in 300 mL of dry THF at 0 °C was added dropwise with stirring a solution of 14.0 g (57 mmol) of **6** in 80 mL of THF. After 30 min, a solution of 9.77 g (57 mmol) of benzyl bromide in 50 mL of THF was added dropwise, and the resulting mixture was allowed to warm to rt and was stirred for 16 h. A few drops of MeOH was added carefully to decompose excess potassium hydride and 25 mL of a saturated aqueous solution of NH_4Cl was added. The organic layer was separated, washed with brine (50 mL), dried over $MgSO_4$ and evaporated to give 18.5 g (97%) of **7** as a pale green oil which was homogeneous by TLC. Column chromatography on basic alumina with 3:7 EtOAc:hexane or distillation at 155-156.5 °C (0.25 mm Hg) gave **7**: IR 2910, 1450, 1370, 1075, 725, 690 cm^{-1}; ^1H NMR δ 1.20 (t, J = 7.0 Hz, 3H), 1.26 (s, 3H), 1.31 (d, J = 5.0 Hz, 3H), 1.59 (m, 2H), 1.60 (s, 3H), 1.68 (s, 3H), 1.91 (m, 2H), 2.07 (m, 2H), 3.40-3.80 (m, 4H), 4.40 (s, 2H), 4.68 (q, J = 5.0 Hz, 1H), 5.12 (m, 1H), 7.25 - 7.40 (m, 5H); ^{13}C NMR δ 15.3, 17.6, 19.9, 22.3, (23.5, 23.5), 25.7, 37.9, (38.6, 38.6), (60.6, 60.7), 61.4, 63.1, 76.0, 99.6, 124.4, 127,0, 127.1, 128.2, 131.4, 139.6. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.24. Found: C, 75.30; H, 10.26.

(4*R*)-4,8-Dimethyl-4-benzyloxy-7,9-dioxaundecan-1-ol (8). Through a solution of 1.5 g (4.5 mmol) of **7** in 99:1 CH_2Cl_2:pyridine[10] at - 78 °C was bubbled ozone for 15 min, by which time TLC indicated disappearance of **7** and formation of one product. The mixture was allowed to warm to 0 °C while argon was bubbled through it, and then 0.17 g (2.2 mmol) of thiourea[21] in 10 mL of methanol was added in one portion, resulting in formation of a precipitate. The mixture was stirred for 1 h at 0 °C, the solvents were evaporated, and the residue was taken up in dry ether and filtered through a celite pad. The filtrate was added dropwise to a suspension of 0.51 g (13 mmol) of $LiAlH_4$ in 100 mL of ether at 0 °C. The mixture was then stirred at rt for 16 h, followed by addition of 1 mL of H_2O, 1mL of 10% aqueous NaOH solution, and 10 mL of H_2O. The organic layer was separated, washed with 10-mL portions of saturated aqueous $CuSO_4$ solution until a deep blue color no longer persisted, washed with brine (10 mL), dried over $MgSO_4$, and evaporated to afford 1.11 g (80%) of **8** as a colorless oil which was homogeneous by TLC. Column chromatography on basic alumina with 3:1 EtOAc:hexane gave **8**: IR 3420, 2930, 1455, 1375, 1050, 745, 700 cm^{-1}; ^1H NMR δ 1.20 (t, J = 6.5 Hz, 3H), 1.27 (s, 3H), 1.31 (d, J = 5.3 Hz, 3H), 1.55-1.90 (m, 6H), 2.60 (bs, 1H), 3.35-3.80 (m, 6H), 4.40 (s, 2H), 4.68 (q, J = 5.3 Hz, 1H), 7.15-7.40 (m, 5H); ^{13}C NMR δ 15.1, 19.7, 23.3, 26.7, 34.9, 37.7, 60.6, 61.2, 62.7, 63.2, 75.9, 99.5, 127.0, 127.1, 128.1, 139.1. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.55; H, 9.71.

(4*R*)-4-Benzyloxy-4,8-dimethyl-1-(phenylseleno)-7,9-dioxaundecane (9). A flask containing 1.43 g (4.57 mmol) of **8**, 2.76 g (9.14 mmol) of N-(phenylseleno)phthalimide,[9] and 25 mL of freshly distilled dry CH_2Cl_2 was subjected to a vacuum freeze-thaw cycle to remove all dissolved gases, then was warmed to 0 °C and 1.85 g (2.28 mL, 9.14 mmol) of freshly distilled tri-*n*-butylphosphine was added neat, dropwise. The mixture was stirred at 0 °C for 4 h, and at rt for 6 h, after which time TLC (3:7 ether:hexane) showed no **8**. The solvent was evaporated, and to the residue was added 20 mL of 3:7 ether:hexane. The undissolved material (diphenyldiselenide) was removed by filtration, the filtrate was evaporated, and the residue was subjected to dry column chromatography on silica gel with 3:7 ether:hexane to give 1.78 g (87%) of crude **9**, still contaminated by some diphenyldiselenide. Column chromatography on silica gel with 3:7 EtOAc:hexane

of a different sample of **9** thus prepared afforded an analytical sample: IR 2930, 1580, 1450, 1370, 1050, 730, 690 cm^{-1}; ^1H NMR δ 1.19 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.29 (d, J = 5.7 Hz, 3H), 1.63-1.97 (m, 6H), 2.92 (t, J = 6.9 Hz, 2H), 3.40-3.75 (m, 4H), 4.37 (s, 2H), 4.66 (q, J = 5.7 Hz, 1H), 7.20-7.50 (m, 10H); ^{13}C NMR δ 15.3, 19.9, (23.6, 23.6), 24.2, 28.4, 37.9, 38.6, (60.7, 60.7), 61.3, 63.2, 75.8, 99.7, 126.7, 127.1, 127.2, 128.2, 129.0 130.4, 132.4, 139.3. LRMS *m/z* 450 (M^+), 404, 377, 361, 343, 297, 271, 253, 221, 184, 157. Anal. Calcd for $C_{24}H_{34}O_3Se$: C, 64.13; H, 7.62. Found: C, 63.93, H, 7.69.

(*R*)-3-Benzyloxy-3-methyl-6-(phenylseleno)hexan-1-ol (10). To 50 mL of CH_2Cl_2 was added 10 g of 70-230 mesh silica gel and then 4 M aqueous HCl solution was added dropwise with rapid stirring until no more acid was adsorbed onto the silica.[13] The resulting slurry was cooled to 0 °C and a solution of the 1.78 g of impure **9** in 15 mL of CH_2Cl_2 was added in one portion. The mixture was stirred at 0 °C for 1 h, after which time TLC (EtOAc) showed no **6**, evaporated, and the dry silica gel residue was flash eluted with 1:1 EtOAc:hexane to afford 0.770 g (44% from **8**) of **10** as a colorless oil which was homogeneous by TLC: IR 3400, 2920, 1580, 1480, 1455, 1440, 1380, 1050, 730, 695 cm^{-1}. ^1H NMR δ 1.31 (s, 3H), 1.62-2.00 (m, 6H), 2.95 (m, 3H), 3.69-3.90 (m, 2H), 4.40 (s, 2H), 7.15-7.55 (m, 10H). ^{13}C NMR δ 23.0, 24.1, 28.2, 38.1, 39.9, 59.2, 63.4, 78.1, 126.7, 127.2, 127.3, 128.3, 128.9, 130.1, 132.4, 138.6. Anal. Calcd for $C_{20}H_{26}O_2Se$: C, 63.65; H, 6.94. Found: C, 63.56; H, 6.97.

(*R*)-3-Benzyloxy-3-methyl-5-hexen-1-ol (11). To a solution of 0.675 g (1.79 mmol) of **10** and 1.25 mL (5 eq) of diisopropylamine[15] in 20 mL of $CHCl_3$ was added a solution of 0.59 g (2.14 mmol) of N-(*p*-toluenesulfonyl)phenyloxaziridine[14] in 10 mL of $CHCl_3$ at 0 °C with stirring. Stirring was continued at 0 °C for 1.5 h, and at rt for 20 h, followed by heating at reflux for 1 h. Evaporation of solvent afforded 1.27 g of residue which was subjected to flash chromatography on silica gel with 2:1 EtOAc:hexane to afford 0.404 g (100%) of **11** as a colorless oil: IR 3400, 2920, 1640, 1455, 1380, 1050, 915, 735, 695 cm^{-1}. ^1H NMR δ 1.33 (s, 3H), 1.65-2.02 (m, 2H), 2.45 (m, 2H), 2.90 (s, 1H), 3.82 (m, 2H), 4.49 (s, 2H), 4.95-5.30 (m, 2H), 5.83 (m, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR δ 22.8, 40.0, 42.9, 59.4, 63.7, 78.5, 118.1, 127.4, 127.4, 128.4, 133.7, 138.7. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.10; H, 8.99.

(*R*)-3-Benzyloxy-3-methylhex-5-enoic acid (12). To a suspension of 6.4 g (17 mmol) of pyridinium dichromate in 10 mL of DMF[16] was added in one portion a solution of 0.316 g (1.43 mmol) of **11** in of 5 mL of DMF. The resulting mixture was stirred at rt for 36 h and then poured into 100 mL of H_2O. Extraction with EtOAc (10x10 mL) and evaporation of solvent gave an oil which was filtered in through a silica Sep-Pak cartridge (Waters) to remove residual chromium salts, evaporated, and dried at 0.5 mmHg for 3 h, to give 0.225g (67%) of **12** as a colorless oil which was homogeneous by TLC: IR 3700, 1731, 1030 cm^{-1}.^1H NMR δ 1.44 (s, 3H), 2.20-2.80 (m, 4H), 4.57 (s, 2H), 5.10-5.25 (m, 2H), 5.84 (m, 1H), 7.30-7.40 (m, 5H), 10.0 (b, 1H). ^{13}C NMR δ 23.0, 42.5, 43.9, 64.3, 77.2, 119.4, 127.7, 127.9, 128.6, 132.5, 137.6, 179.3. HRMS (FAB): Calcd for $C_{14}H_{19}O_3$ (M+H): 235.1334. Found: 235.1333.

(*R*)-3-Benzyloxy-3-methylpentanolide (13). A solution 0.218 g (0.93 mmol) of **12** in 20 mL of 4:1 MeOH:CH_2Cl_2 was ozonized at -78 °C for 5 min. The ozone was replaced by argon, the mixture was warmed to rt, and the solvents were evaporated and replaced by 10 mL of MeOH. The resulting solution was cooled to 0 °C and 0.08 g (2.1 mmol) of $NaBH_4$ powder was added in one portion. The mixture was stirred for 20 h at 0 °C, poured into 50 mL of brine, extracted with 10x10 mL of chloroform, dried over $MgSO_4$, evaporated, and dried at 0.5 mmHg for 3 h to afford 0.146 g (71%) of **13** as a waxy, colorless oil which was

homogeneous by TLC: IR 1730, 1265, 1125, 1065, 750, cm^{-1}; ^1H NMR δ 1.42 (s, 3H), 1.91 (m, 1H), 2.13 (m, 1H), 2.49 (d, J = 17.2 Hz, 1H), 2.93 (dd, J = 17.2, 2.2 Hz, 1H), 4.31 (m, 1H), 4.46 (ABq, J = 11.2 Hz, Δν = 6.3 Hz, 2H), 4.56 (m, 1H), 7.25-7.40 (m, 5H); the multiplets at δ 1.91 ($H_{4\alpha}$), 2.13 ($H_{4\beta}$), 4.31 ($H_{5\alpha}$), and 4.56 ($H_{5\beta}$) could be accurately simulated by use of the LAOCOON III program[22] with $J_{2\beta4\beta}$ = 2.2 Hz, $J_{4\beta4\alpha}$ = 14.4 Hz, $J_{4\beta5\beta}$ = 3.8 Hz, $J_{4\beta5\alpha}$ = 3.5 Hz, $J_{4\alpha5\beta}$ = 11.2 Hz, $J_{4\alpha5\alpha}$ = 5.4 Hz, and $J_{5\beta5\alpha}$ = 11.2 Hz; ^{13}C NMR δ 24.5, 33.8, 42.1, 64.1, 65.7, 72.6, 127.2, 127.6, 128.5, 138.1, 170.0. HRMS (FAB): Calcd for $C_{13}H_{17}O_3$ (M+H): 221.1178. Found: 221.1180.

(*R*)-Mevalonolactone (1). According to the procedure of Bieg and Szeja,[18] to a solution of 42.1 mg (0.191 mmol) of **13** in 4 mL of MeOH was added 100 mg of 10% palladium-on-carbon and 50 mg (0.79 mmol) of ammonium formate. The resulting mixture was heated at reflux for 2 h, after which time TLC (9:1 EtOAc: hexane) showed one spot with the R_f of (*R,S*)-**1**, filtered while hot under argon, and the filter pad was washed with 2 x 1 mL of MeOH. The combined filtrates were evaporated to give 24.4 mg of colorless oil, which was purified by Kugelrohr distillation (ot 180 °C, 0.25 mmHg) to yield 21.8 mg (88%) of **1**, which was homogeneous by TLC: ^1H NMR identical with that of an authentic sample of (*R,S*)-**1**.

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