# NOVEL SYNTHESIS OF (4*R*)-4-METHYLPENTANOLIDE FROM (L)-(-)-MENTHOL

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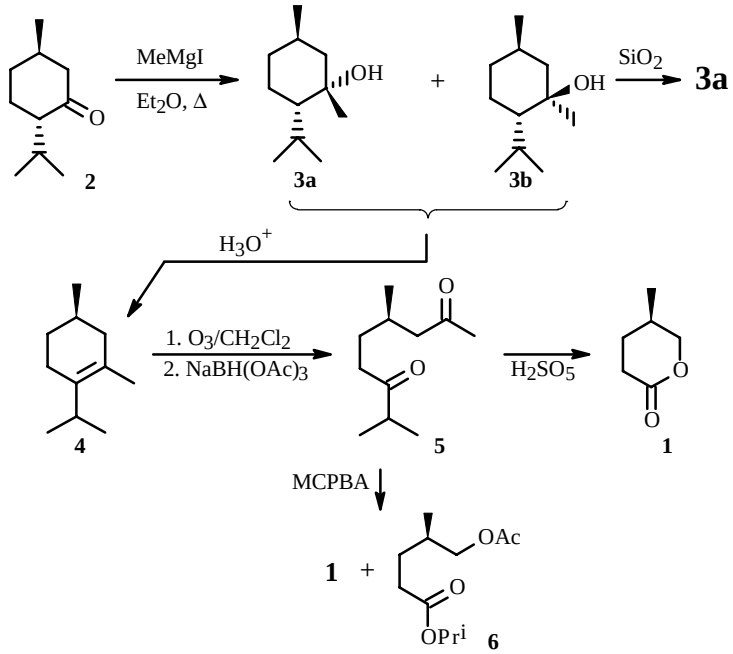
*A novel synthesis of the promising optically pure chiral (4R)-4-methylpentanolide that is based on several regiospecific oxidative transformations of (4R)-2,4-dimethyl-1-(1-methylethyl)-1-cyclohexene, the product of addition of (-)-menthone and methylmagnesium iodide followed by acid dehydration, was proposed.*

**Key words:** L-(-)-Menthol, (-)-menthone, (4*R*)-4-methylpentanolide, chiral synthon, (1*S*,2*S*,5*R*)- and (1*R*,2*S*,5*R*)-1,5-dimethyl-2-(1-methylethyl)cyclohexan-1-ols, (4*R*)-2,4-dimethyl-1-(1-methylethyl)-1-cyclohexene, (4*R*)-4,8-dimethylnonan-2,7-dione, isopropyl-(4*R*)-5-acetoxy-4-methylpentanoate.

In continuation of research on functionalization of the common natural monoterpenoid L-(-)-menthol (*ee* ~ 100%), we developed a synthesis of (4*R*)-4-methylpentanolide (**1**), a potentially useful chiral synthon.

Lactone **1** was previously prepared as the racemate by oxidation of 3-methyltetrahydropyran with sodium bromate [1] or dimethyl- or methyltrifluoromethyldioxiranes [2]. It was isolated in the optically active form from side products of industrial production of dehydropregnenolone acetate from diosgenin [3-5] and cyclization of 5-amino-4*R*-methylpentanoic acid [6].




$H_3O^+ = (CO_2H)_2$, or $H_3PO_4$, or $H_2SO_4$

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According to the literature [7, 8], Grignard addition of methylmagnesium iodide to (1*R*,4*S*)-(-)-menthone (**2**) in THF at room temperature occurs stereoselectively and produces a mixture of (1*S*,2*S*,5*R*)- (**3a**) and (1*R*,2*S*,5*R*)-1,5-dimethyl-2-(1-methylethyl)cyclohexan-1-ol (**3b**) with primarily the former (90%) and 65% yield without catalyst [7] and 69% yield with $CeCl_3$ catalyst [8]. Carrying out the reaction with boiling in $Et_2O$ enabled the overall yield of the desired alcohols to be increased to 96% and the stereoselectivity to reach 94:6 (**3a**:**3b**).

Acid dehydration of the mixture of alcohols (**3a** and **-b**) occurs over 24 h to produce the thermodynamically more stable (4*R*)-2,4-dimethyl-1-(1-methylethyl)-1-cyclohexene (**4**), the structure of which was indirectly confirmed by ozonolytic decomposition of its double bond. After reduction of the peroxide ozonolysis products with sodium trisacetoxyborohydride, which converts 1-methylcycloalkenes into hydroxyketones without affecting the ketone formed [9], (4*R*)-4,8-dimethylnonan-2,7-dione (**5**) was obtained as the only product.

Exhaustive oxidation of diketone **5** by Caro acid according to Baeyer and Villiger [10, 11] occurs regiospecifically and gives the desired optically active lactone **1** with rotation angle 16.8° (+14.3°, o.p. 85% [3] and +16.8°, o.p. 100% [4]). Lactone **1** spontaneously converts on storage for a month from an oil into a crystalline substance owing to formation of linear polyesters [4, 5]. This is accompanied by a decrease in the rotation angle to +4.7° ($[\alpha]_D^{21}$ +8.1° [4] and $[\alpha]_D^{20}$ +5.3° [5]).

Formation of lactone **1** through the intermediate diester **6** was confirmed by spectral analysis ($^{13}C$ NMR) of the chromatographically unseparated mixture (1:1) of these compounds that was formed upon oxidation of dione **5** by metachloroperbenzoic acid.

## EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in thin layers. NMR spectra were recorded on a Bruker AM-300 spectrometer (working frequency 300.13 MHz for PMR and 75.47 MHz for $^{13}C$ NMR) in $CDCl_3$. The internal standards were the impurity protons in $CDCl_3$ with δ 7.27 ppm in the PMR; the average signal of $CDCl_3$ at δ 77.00 ppm in the $^{13}C$ NMR. Signals in the PMR were assigned using double resonance and two-dimensional homonuclear correlation spectroscopy COSY H—H. GC was performed on Chrom-5 [column length 1.2 m, stationary phase silicone SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm), working temperature 50-300°C] and Chrom-41 [column length 2.4 m, stationary phase PEG-6000, working temperature 50-200°C] instruments with He carrier gas. Column chromatography was carried out on silica gel L (Czech Rep., 40-100 μm). TLC was performed on Silufol UV-254 (Czech Rep.) plates. Optical rotation was measured on a Perkin—Elmer 241-MC polarimeter. Starting menthone was synthesized as before [12]. Elemental analyses of all compounds agreed with those calculated.

**(1*S*,2*S*,5*R*)- and (1*R*,2*S*,5*R*)-1,5-Dimethyl-2-(1-methylethyl)cyclohexan-1-ols (3).** Grignard reagent was prepared from Mg (1.84 g, 77.0 mg-at) and methyliodide (10.86 g, 77.0 mmol) in absolute $Et_2O$ (38 mL) and treated dropwise with menthone (**2**, 10.00 g, 65.0 mmol) at 0°C under Ar. The mixture was boiled for 1 h, held for 12 h at room temperature, cooled to 0°C, treated with $H_2O$ (10 mL), and stirred for 1 h at room temperature. The solid was filtered off and washed on a Schott filter with $Et_2O$ (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to afford a mixture (94:6) of **3a** and **3b** (10.61 g, 96%), the main component of which (**3a**) was isolated by column chromatography over $SiO_2$ (hexane:$Et_2O$, 7:3), $R_f$ 0.47 (hexane:$Et_2O$, 7:3), $[\alpha]_D^{20}$ -2.44 (*c* 2.5, $CHCl_3$). IR spectrum (KBr, ν, $cm^{-1}$): 3600-3350 (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.84 (3H, d, J = 2, $CH_3C$-5), 0.88 and 0.89 [6H, both d, J = 2, $(C\underline{H}_3)_2CH$], 1.01-1.05 (1H, m, $H_a$-6), 1.04-1.08 (1H, m, H-2), 1.05-1.09 (1H, m, $H_a$-3), 1.18-1.27 (1H, m, $H_e$-3), 1.22 (3H, s, $CH_3C$-1), 1.30-1.39 (1H, m, $H_e$-6), 1.34-1.40 (1H, m, $H_a$-4), 1.45-1.50 (1H, m, H-5), 1.60-1.78 [1H, m, $(CH_3)_2C\underline{H}$], 1.75-1.80 (1H, m, $H_e$-4), 3.20 (1H, br.s, OH), [8].

$^{13}C$ NMR spectrum, **3a** epimer ($CDCl_3$): 19.17 (q, $CH_3C$-5), 22.03 and 22.30 [both q, $(\underline{C}H_3)_2C$], 24.58 (d, C-5), 24.58 (t, C-3), 25.41 [d, $(CH_3)_2\underline{C}$], 30.67 (q, $CH_3C$-1), 35.20 (t, C-4), 52.91 (t, C-6), 53.14 (d, C-2), 74.08 (s, C-1). $^{13}C$ NMR, **3b** epimer (from a mixture of **3a** and **3b**) ($CDCl_3$): 18.18 (q, $CH_3C$-5), 20.84 (t, C-3), 22.24 and 23.75 [both q, $(\underline{C}H_3)_2C$], 26.08 (d, C-5), 28.81 (q, $CH_3C$-1), 28.85 [d, $(CH_3)_2\underline{C}$], 35.18 (t, C-4), 50.45 (d, C-2), 50.69 (t, C-6), 72.98 (s, C-1).

**(4*R*)-2,4-Dimethyl-1-(1-methylethyl)-1-cyclohexene (4). a.** A mixture of **3a** and **3b** (2.00 g, 12.0 mmol) and oxalic acid (1.62 g, 18.0 mmol) was held for 24 h at 100°C, cooled, diluted with hexane (20 mL), washed successively with saturated $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$, and evaporated to afford **4** (1.64 g, 90%), $[\alpha]_D^{20}$ +9.0° (*c* 2.5, $CHCl_3$).

IR spectrum (KBr, ν, $cm^{-1}$): 1645 (C=C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, d, $^3J$ = 6.7, $CH_3$C-4), 0.92 [6H, d, $^3J$ = 6.9, $(CH_3)_2$C], 1.28 (1H, dd, $^2J$ = 7.3, $^3J$ = 6.7, $H_a$-5), 1.61 (3H, s, $CH_3$C-2), 1.60-1.69 (1H, m, $H_e$-5), 1.88 (1H, dd, $^2J$ = 6.4, $^3J$ = 2.0, $H_a$-6), 1.94 (1H, dd, $^2J$ = 6.5, $^3J$ = 10.5, $H_a$-3), 1.90-1.98 (1H, m, $H_a$-4), 1.92-2.02 (1H, m, $H_e$-6), 2.29 (1H, d, $^2J$ = 6.5, $H_e$-3), 2.82 [1H, s, $(CH_3)_2$C<u>H</u>].

$^{13}$C NMR spectrum ($CDCl_3$): 18.60 (q, $CH_3$C-4), 20.27 and 21.91 [both q, (<u>C</u>$H_3)_2$C], 23.31 (t, C-6), 29.18 (d, C-4), 29.46 [d, $(CH_3)_2$<u>C</u>], 31.78 (t, C-5), 41.24 (t, C-3), 123.97 (s, C-2), 134.37 (s, C-1), 207.6 (q, $CH_3$C-2).

**b.** A mixture of **3a** and **3b** (2.00 g, 12.0 mmol) and $H_3PO_4$ (0.45 mL, 85%) was worked up as described in **a.** to afford **4** (1.64 g, 90%) that had identical spectral data as the product from that experiment.

**c.** A solution of **3a** and **3b** (2.00 g, 12.0 mmol) and conc. $H_2SO_4$ (1 mL) in $H_2O$ (10 mL) and the method described in **a.** afforded **4** (1.66 g, 91%) that was identical to the product from **a.**

**(4*R*)-4,8-Dimethyl-2,7-nonanedione (5).** An ozone—oxygen mixture (ozonator production 40.0 mmol $O_3$/h) was passed through a solution of **4** (5.00 g, 33.0 mmol) and glacial acetic acid (3.93 g, 66.0 mmol) in $CH_2Cl_2$ (91 mL) with stirring at -4 to -2°C until 34.0 mmol of ozone had been absorbed. The reaction mixture was purged with Ar, diluted with $CH_2Cl_2$ (46 mL), stirred (10°C), treated with a previously prepared suspension of $NaBH(OAc)_3$ [prepared by adding glacial acetic acid (27.14 g, 452.0 mmol) in $CH_2Cl_2$ (46 mL) to a suspension of $NaBH_4$ (5.74 g, 151.0 mmol) in $CH_2Cl_2$ (228 mL) with stirring for 2 h], heated to room temperature, stirred for 3 h, cooled to 10°C, and treated with NaOH solution (10.31 g in 229 mL $H_2O$). The organic layer was separated, washed successively with saturated $NH_4Cl$ solution and water, dried over $Na_2SO_4$, and evaporated to afford **5** (4.75 g, 79%), $[\alpha]_D^{20}$ +8.88° (*c* 2.5, $CHCl_3$).

IR spectrum (KBr, ν, $cm^{-1}$): 1712 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.88 (3H, d, J = 2.0, $CH_3$C-4), 1.08 [6H, d, J = 2.0 $(CH_3)_2$C], 2.11 (3H, s, H-1), 0.93-1.00 (2H, m, H-5), 1.15-1.65 (1H, m, H-4), 2.15-2.65 [5H, m, H-3, H-6, $(CH_3)_2$C<u>H</u>].

$^{13}$C NMR spectrum ($CDCl_3$): 18.33 [q, (<u>C</u>$H_3)_2$C], 19.64 (d, $CH_3$C-4), 28.86 (q, C-1), 30.41 (d, C-4), 30.58 (t, C-5), 37.91 (t, C-6), 40.87 (d, C-8), 51.07 (t, C-3), 208.53 (s, C-2), 214.55 (s, C-7).

**(4*R*)-4-Methylpentanolide (1).** Concentrated $H_2SO_4$ (8.1 mL) was added to water (2.7 mL). The mixture was cooled to 5°C, treated with $K_2S_2O_8$ (5.67 g, 21.0 mmol), adjusted to 15°C, treated successively with water (8.8 mL) and **5** (1 g, 5.4 mmol), stirred at room temperature for 35 h, poured into cold water (50 mL), and extracted with $CH_2Cl_2$ (3 × 50 mL). The extract was washed successively with saturated $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$, and evaporated to afford lactone **1** (0.41 g, 66%), $[\alpha]_D^{20}$ +16.8° (*c* 1.0, $CHCl_3$).

IR spectrum (KBr, ν, $cm^{-1}$): 1748 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, d, $J_3$ = 6.6, $CH_3$C-5), 1.44 (1H, ddt, $^2J$ = 12.8, $^3J$ = 13.4, $^3J$ = 7.1, $H_a$-4), 1.83-1.89 (1H, m, $H_e$-3), 1.90-1.94 (1H, m, H-4), 2.38 (1H, ddd, $^2J$ = 15.7, $^3J$ = 13.4, $^3J$ = 7.1, $H_e$-3), 2.51 (1H, ddd, $^2J$ = 15.7, $^3J$ = 4.3, $^3J$ = 7.0, $H_a$-3), 3.80 (1H, dd, $^2J$ = 12.7, $^3J$ = 13.7, $H_a$-5), 4.19 (1H, ddd, $^2J$ = 12.7, $^3J$ = 4.0, $^3J$ = 1.1, $H_e$-5).

$^{13}$C NMR spectrum ($CDCl_3$): 16.02 (q, $CH_3$-5), 25.58 (t, C-4), 27.32 (d, C-5), 29.91 (t, C-3), 170.84 (s, C-2).

**(4*R*)-4-Methylpentanolide (1) and Isopropyl-(4*R*)-4-methyl-5-acetoxypentanoate (6).** A suspension of *m*-chloroperbenzoic acid (1.41 g, 8.2 mol, 50%) in dry $CHCl_3$ (7.5 mL) was treated with diketone **5** (0.5 g, 2.7 mol) in dry $CHCl_3$ (2.3 mL); stirred at room temperature for 3 d; diluted with $CHCl_3$ (100 mL); washed with saturated $Na_2S_2O_3$, $NaHCO_3$, and NaCl solutions; dried over $Na_2SO_4$, and evaporated to afford a mixture (1:1, 0.7 g) of the *(R)*-4-methylpentanolide (**1**) and isopropyl-(*R*)-4-methyl-5-acetoxypentanoate (**6**).

IR spectrum (KBr, ν, $cm^{-1}$): 1748 (C=O).

$^{13}$C NMR spectrum, **6**: (from a mixture of **1** and **6**) ($CDCl_3$): 16.40 (q, $CH_3$-4), 20.83 (q, <u>C</u>$H_3$COO), 21.74 [q, (<u>C</u>$H_3)_2$C], 28.42 (t, C-3), 32.03 (d, C-4), 32.61 (t, C-2), 67.50 [d, $(CH_3)_2$<u>C</u>], 68.77 (t, C-5), 171.07 (s, $CH_3$<u>C</u>OO), 172.95 (s, C-1).

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