Chemistry of Natural Compounds, Vol. 40, No. 5, 2004

NEW APPROACH TO THE SYNTHESIS OF (*R*)-3-METHYL-γ-BUTYROLACTONE

R. Ya. Kharisov,[1] E. R. Latypova,[2] R. F. Talipov,[1] G. Yu. Ishmuratov,[1] and G. A. Tolstikov[1]

UDC 547.473.2+547.596.4+ 542.943+542.957

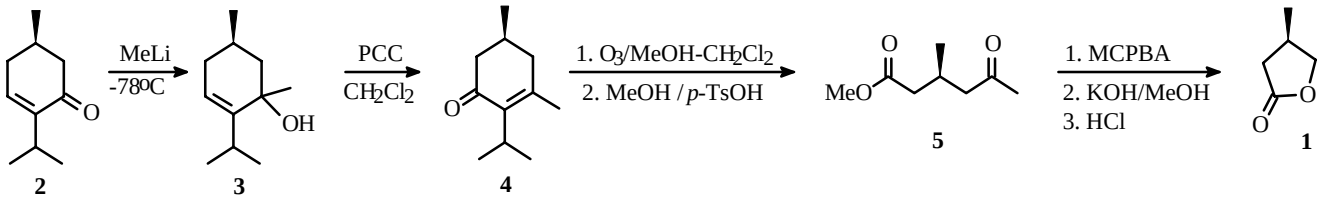
*Optically active pure (*R*)-3-methyl-γ-butyrolactone was synthesized from (*R*)-4-menthenone.*

Key words: (*R*)-3-methyl-γ-butyrolactone, (*R*)-4-menthenone, (*S*)-3,5-dimethyl-2-isopropyl-2-cyclohexen-1-one, methyl (*S*)-3-methyl-5-oxohexanoate, ozonolysis, Cr(VI) oxidation, Baeyer—Villager reaction.

Optically active β-methyl-γ-butyrolactone is used as an intermediate in the synthesis of vitamins E and K and dolichol and its analogs [1]. It also possesses antiveratrin activity and can be used in pharmacology [2].

Known methods for synthesizing (*R*)-3-methyl-γ-butyrolactone (**1**) are Baeyer—Villager oxidation of esters of optically active β-methyl-ε-ketocarboxylic acids [1] and cyclopropanation of (*E*)-(2*R*,3*S*)-6-methyl-3,4-dimethyl-2-phenylperhydro-1,4-oxazepin-5,7-dione with subsequent hydrolysis [3].

We proposed an approach to the title lactone (**1**) starting with (*R*)-4-menthenone (**2**). We used **2** because of its availability from *l*-(-)-menthol [4] and its 100% optical purity. The method is based on regioselective 1,2-addition of LiMe to **2** with subsequent work up of the resulting tertiary alcohol (**3**) with pyridinium chlorochromate (PCC). Ozonolytic cleavage of the resulting (*S*)-5-methylmenthenone (**4**) with subsequent methanolysis gave ketoester **5**. The synthesis was completed in one flask by sequential Baeyer—Villager oxidation of **5**, basic saponification of the reaction mixture, and acidolysis to give (*R*)-3-methyl-γ-butyrolactone (**2**) in overall yield of 33% calculated based on **2**.



EXPERIMENTAL

IR spectra were recorded on a Specord M-82 instrument as thin layers. NMR spectra (δ, ppm, J/Hz) were obtained on a Bruker AM-300 spectrometer (working frequency 300.13 MHz for PMR and 75.47 MHz for ^{13}C) in $CDCl_3$ relative to TMS. Chromatography was performed on a Chrom-5 instrument [column length 2.4 m, stationary phase PEG-6000 (5%) on Inerton AW-DMCS (0.125-0.160 mm), working temperature 50-200°C] with He carrier gas. Optical rotation was measured on a Perkin—Elmer 241-MC polarimeter. Solvents were dried by the usual methods [5]. Column chromatography was carried out over SiO_2 (L, 60-200 μm, Lancaster, England). TLC was performed on SiO_2 (Silufol, Czech Rep.). Petroleum ether (PE, bp 40-70°C) was used for chromatography.

1) Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, Ufa, pr. Oktyabrya, 71, fax (3472) 35 60 66, e-mail: kharis@anrb.ru; 2) Bashkiriya State University, 450074, Ufa, ul. Frunze, 32, fax (3472) 22 61 05, e-mail: TalipovRF@bsu.bashedu.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 396-397, September-October, 2004. Original article submitted July 26, 2004.

 0009-3130/04/4005-0482

(*S*)-3,5-Dimethyl-2-isopropyl-2-cyclohexen-1-one (4). A stirred solution of **2** (3.00 g, 19.7 mmol) in absolute Et_2O (30 mL, -78°C, Ar) was treated dropwise with LiMe in absolute THF (34 mL, 1.75 N). The reaction mixture was stirred as the temperature was increased gradually over 1 h to ambient and then for another 2 h at room temperature, cooled to 5°C, treated with saturated NH_4Cl solution, stirred for 1.5 h, and extracted with Et_2O (3 × 30 mL). The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated to afford **3** (2.83 g, 85%).

IR spectrum (ν, cm^{-1}): 916, 994 (H–C=); 1162 (C–O); 1654 (C=C); 3460 (OH). Compound **3** was used without further purification in the next step.

A suspension of PCC (7.93 g, 36.7 mmol) in dry CH_2Cl_2 (20 mL, 5-10°C, Ar) was stirred vigorously and treated with **3** (2.80 g, 16.7 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred for 2 h at room temperature, treated with Et_2O (30 mL), stirred for another 15 min, and filtered through a layer of Al_2O_3. The solid was washed with Et_2O. The filtrate was evaporated. The solid was chromatographed over SiO_2 (PE eluent) to afford **4** (2.02 g, 62% based on **2**). The chemical purity according to GC was 96%, R_f 0.67 (PE:EA, 2:1), $[\alpha]_D^{21}$ +119.0° (*c* 7.1, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 1618 (C=C), 1666 (C=O).

PMR spectrum (δ, ppm, J/Hz): 0.98 (d, 3H, J = 5.8, CH_3C-5), 1.12 and 1.15 [both d, 6H, J = 7.1, $(CH_3)_2$C], 1.92 (s, 3H, CH_3C-3), 1.93-2.11 (m, 3H, H_a-4, H-5, H_a-6), 2.27 (d, 1H, J = 13.8, H_e-6), 2.38 (d, 1H, J = 12.7, H_e-4), 2.95 (h, 1H, J = 7.1, HCC-2).

^{13}C NMR spectrum (δ, ppm): 20.38 ($\underline{C}H_3$C-5), 20.90 and 21.15 [($\underline{C}H_3)_2$C], 21.26 (H$\underline{C}$C-2), 27.10 ($\underline{C}H_3$C-3), 29.41 (C-5), 42.26 (C-4), 47.24 (C-6), 139.75 (C-2), 153.38 (C-3), 199.31 (C-1).

Methyl (*S*)-3-Methyl-5-oxohexanoate (5). An O_3/O_2 mixture (produced by an ozonator at 40 mmol O_3/h) was passed through a solution of **4** (1.40 g, 8.5 mmol) in a mixture of dry MeOH (10 mL) and CH_2Cl_2 (10 mL) at 5°C until the starting material completely dissolved (TLC monitoring). The reaction mixture was purged with Ar, treated with TsOH (0.08 g) and dry MeOH (15 mL), stirred for 48 h at room temperature, treated with $NaHCO_3$ (0.84 g), evaporated in vacuum, diluted with Et_2O (100 mL), washed with saturated NaCl solution until the pH was 7, dried over Na_2SO_4, evaporated, and chromatographed over SiO_2 to afford **5** (1.00 g, 78%). The chemical purity was 99% according to GC, R_f 0.54 (PE:*t*-BuOMe, 2:1), $[\alpha]_D^{21}$ +2.57° (*c* 1.29, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 1264 (C–O–C); 1714, 1738 (C=O).

PMR spectrum (δ, ppm, J/Hz): 0.98 (d, 3H, J = 6.5, $\underline{C}H_3$C-3), 2.14 (s, 3H, H-6), 2.17-2.57 (m, 5H, H-2, H-3, H-4), 3.66 (s, 3H, CH_3O).

(*R*)-3-Methyl-γ-butyrolactone (1). A suspension of *m*-chloroperbenzoic acid (1.10 g, 6.3 mmol) in $CHCl_3$ (30 mL) at room temperature was treated dropwise with **5** (1.00 g, 42 mmol) in $CHCl_3$ (20 mL). The reaction mixture was stirred at room temperature for 48 h, diluted with Et_2O, washed successively with Na_2SO_3 solution (5%) and saturated $NaHCO_3$ and NaCl, dried over $MgSO_4$, and evaporated.

The solid (0.60 g) was treated with KOH (0.71 g, 12.6 mmol) dissolved in MeOH (5 mL), stirred at room temperature for 48 h, and boiled for 4 h. The MeOH was evaporated. The mixture was treated with HCl (6 N) until the pH was 3-4, extracted with *t*-BuOMe, dried over Na_2SO_4, and evaporated. The solid was chromatographed over SiO_2 to afford **1** (0.43 g, 68%), R_f 0.43 (PE:*t*-BuOMe, 2:1), $[\alpha]_D^{20}$ +25° (*c* 4, MeOH) (similar to the reported values [1]). The IR and NMR spectra agreed with those previously reported [6].

REFERENCES

1. Jpn. Pat. No. 60-174535 (1987); *Ref. Zh. Khim.*, 11O51P (1988).
2. D. G. Wenzel and C. M. Smith, *J. Am. Pharm. Assoc.*, **47**, 269 (1958).
3. T. Mukaiyama, K. Fujimoto, T. Hirose, and T. Takeda, *Chem. Lett.*, **6**, 635 (1980).
4. W. Treibs and H. Albrecht, *J. Prakt. Chem.*, **13**, 291 (1961).
5. A. J. Gordon and R. A. Ford, A Chemist's Companion, Wiley-Interscience, New York (1972).
6. E. I. Troyanskii, I. V. Svitan′ko, and G. I. Nikishin, *Izv. Akad. Nauk, Ser. Khim.*, 2318 (1982).