SYNTHESIS OF OPTICALLY PURE 3*R*-METHYLCYCLOPENTAN-1-ONE FROM L-(-)-MENTHOL

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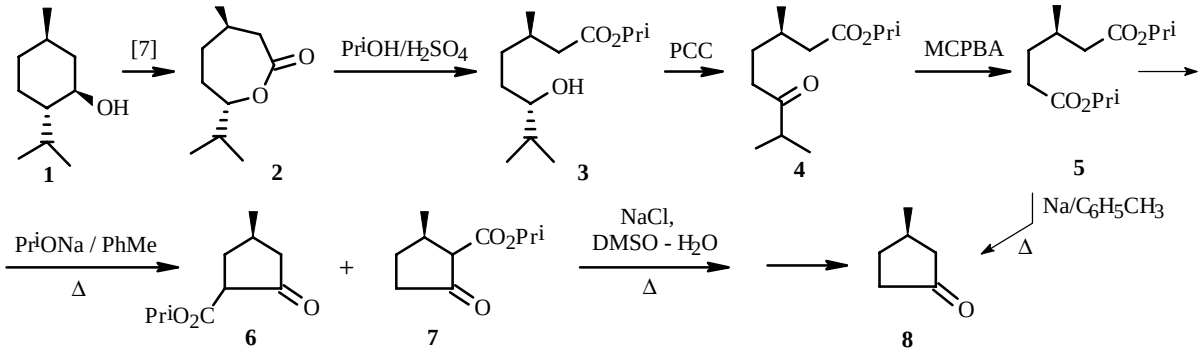
Synthesis of optically pure 3R-methylcyclopentan-1-one using in the key step Dieckmann cyclization of diisopropyl 3R-methylhexan-1,6-dioate, which is accessible from L-(-)-menthol, was proposed.

Key words: L-(-)-menthol, diisopropyl 3*R*-methylhexan-1,6-dioate, isopropyl 4*R*-methyl-2-oxocyclopentan-1-carboxylate, 3*R*-methylcyclopentan-1-one, Dieckmann cyclization.

3*R*-Methylcyclopentan-1-one (**8**) has been used to synthesize oil components of marigold *Tagetes glandulifera*, e.g., (+)-dihydrotagetone [1], and Bulgarian rose oil, e.g., 4*R*-rosoxide [2-(2,2-dimethylvinyl)-4*R*-tetrahydropyran] [2].

Optically active **8** has been prepared previously starting from *R*-pulegone [3] using cyclization of 3*R*-methyl-1,6-hexanedicarboxylic acid in the key step and using decarbalkoxylation of methyl and ethyl esters of 4*R*-methyl-2-oxocyclopentan-1-carboxylic acid [2, 4-6].

We proposed a new approach to the synthesis of optically pure 3*R*-methylcyclopentan-1-one (**8**) that is based on the available monoterpenoid L-(-)-menthol (**1**), which gave mentholactone (**2**) as before [7]. Subsequent transesterification using isopropanol and H_2SO_4 produced isopropyl-3*R*,7-dimethyl-6*S*-hydroxyoctanoate (**3**). Successive Corey and then Bayer—Villager (using MCPBA, which proceeds regiospecifically) oxidations afforded diisopropyl 3*R*-methylhexan-1,6-dioate (**4**), Dieckmann cyclization of which was performed by several methods. Using sodium isopropylate as the base produced a mixture that was inseparable by column chromatography. According to GC and PMR spectra, the ratio of integrated intensities of a doublet at 1.15 ppm for CH_3-4 and a doublet at 1.19 ppm for CH_3-5, which belong to the isopropyl esters of 4*R*-methyl-2-oxo- (**6**) and 5*R*-methyl-2-oxo- (**7**) cyclopentan-1-carboxylic acids, respectively, was 3.5:1. Decarboxylation of the mixture of esters (**6** and **7**) by heating in DMSO in the presence of NaCl [8] gave a single product, 3*R*-methyl-cclopentan-1-one (**8**). An attempt to increase the regioselectivity of the cyclization of **5** by using sodium amide as the base, which was used previously [9] for the dimethyl ester of 3-methylhexan-1,6-dioic acid, was unsuccessful. The starting compound was obtained. Cyclization of **5** in the presence of Na, which was also used to cyclize diesters [10], led to decarboxylation and formation of a single product, **8**.



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Thus, a synthetic scheme for the valuable intermediate 3*R*-methylcyclopentan-1-one that is used to synthesize several biologically active compounds was developed based on the accessible monoterpenoid L-(-)-menthol (**1**) and gave an overall yield of 30% calculated for **1**.

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 standard for PMR was the proton impurity in $CDCl_3$ at δ 7.27 ppm; for ^{13}C NMR, the average $CDCl_3$ signal at δ 77.00 ppm. GC was performed on Chrom-5 [column length 1.2 m, stationary phase silicon SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm), working temperature 50-300°] and Chrom-41 [column length 2.4 m, stationary phase PEG-6000, working temperature 50-200°] instruments with He carrier gas. Column chromatography was carried out on silica gel L (40-100 μm) (Czech Rep.). TLC was performed on Silufol UV-254 plates (Czech Rep.). Optical rotation was measured on a Perkin—Elmer 241-MC polarimeter. Elemental analyses of all compounds agreed with those calculated.

Isopropyl 3*R*,7-Dimethyl-6*S*-hydroxyoctanoate (3). A solution of **2** (2.5 g, 14.7 mmol) obtained from **1** as before [7] in dry isopropanol (19 mL) was acidified with conc. H_2SO_4 (2 drops) and stirred on a magnetic stirrer for 72 h. The isopropanol was evaporated. The solid was dissolved in ethylacetate, washed successively with saturated solutions of NaCl, $NaHCO_3$, and NaCl, dried over $MgSO_4$, and evaporated to afford **3** (2.87 g, 85%), $[\alpha]_D^{20}$ -13.3° (*c* 0.90, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.82 (6H, d, J = 6.8, H-8, CH_3-7), 0.84 (3H, d, J = 6.8, CH_3-3), 1.19 [6H, d, J = 6.8, $(C\underline{H}_3)_2CH$], 1.93 (8H, m, H-2—H-5, H-7), 3.25 (1H, m, H-6), 3.97 (1H, br.s, OH).

^{13}C NMR spectrum ($CDCl_3$): 18.73 (q, C-8, CH_3-7), 19.64 (q, CH_3-3), 21.68 [q, $CH(\underline{C}H_3)_2$], 30.42 (d, C-3), 31.24 (t, C-4), 32.86 (t, C-5), 33.22 (d, C-7), 41.83 (t, C-2), 67.19 [d, $\underline{C}H(CH_3)_2$], 76.63 (d, C-6), 172.67 (s, C-1).

Isopropyl 3*R*,7-Dimethyl-6*S*-oxooctan-1-oate (4). A suspension of PCC (4.18 g, 19.4 mmol) in dry CH_2Cl_2 (75 mL) was treated dropwise with a solution of **3** (2.87 g, 12.4 mmol) in dry CH_2Cl_2 (5 mL), stirred for 3 h, diluted with Et_2O (80 mL), filtered through a layer of Al_2O_3, and evaporated to afford **4** (2.50 g, 83%), $[\alpha]_D^{20}$ +2.8° (*c* 2.82, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 (3H, d, J = 6.1, CH_3-3), 1.07 (6H, d, J = 6.8, CH_3-7, H-8), 1.19 [6H, d, J = 6.1, $(C\underline{H}_3)_2CH$], 1.50 (3H, m, H-3, H-4), 2.22 (5H, m, H-2, H-5, H-7), 4.97 [1H, septet, J = 6.1, $(CH_3)_2C\underline{H}$].

^{13}C NMR spectrum ($CDCl_3$): 18.21 (q, C-8, CH_3-7), 19.41 (q, CH_3-3), 23.86 [q, $(\underline{C}H_3)_2CH$], 30.01 (d, C-3), 30.26 (t, C-4), 37.74 (t, C-5), 40.76 (d, C-7), 41.86 (t, C-2), 67.38 [d, $(CH_3)_2\underline{C}H$], 172.35 (s, C-1), 214.38 (d, C-6).

Diisopropyl 6*R*-Methylhexan-1,6-dioate (5). A suspension of MCPBA (3.10 g, 8.9 mmol) in dry $CHCl_3$ (30 mL) at room temperature was treated dropwise with a solution of **4** (1.40 g, 6.2 mmol) in dry $CHCl_3$ (10 mL), stirred for 48 h, diluted with CH_2Cl_2 (100 mL), washed successively with saturated solutions of $NaHCO_3$, $Na_2S_2O_3$, and NaCl, dried over $MgSO_4$, and evaporated to afford **5** (1.25 g, 83%), $[\alpha]_D^{20}$ +3.1° (*c* 3.20, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.93 (3H, d, J = 6.1, CH_3-3), 1.19 [12H, d, J = 6.1, $(C\underline{H}_3)_2CH$], 4.97 [2H, septet, J = 6.1, $(CH_3)_2C\underline{H}$], 2.06 (m, H-2—H-5).

^{13}C NMR spectrum ($CDCl_3$): 19.18 (q, CH_3-3), 21.72 [q, $(\underline{C}H_3)_2CH$], 30.32 (d, C-3), 30.64 (t, C-4), 41.92, 42.47 (both t, C-2, C-5), 67.39, 67.44 [both d, $(CH_3)_2\underline{C}H$], 172.26 (s, C-6), 173.02 (s, C-1).

Isopropyl 4*R*-Methyl-2-oxo- (6) and 5*R*-Methyl-2-oxo- (7) cyclopentan-1-carboxylates. A solution of sodium isopropylate that was prepared from Na (0.05 g, 2.05 mg-at) and isopropanol (0.13 g, 2.1 mmol) in dry toluene (3 mL) was treated dropwise (Ar) with a solution of **5** (0.50 g, 2.1 mmol) in dry toluene (2 mL). The mixture was boiled for 8 h, cooled to room temperature, and poured into cold water (25 mL) containing CH_3COOH (8.5 mL). The aqueous layer was extracted with ether (3×40 mL), washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, and evaporated to afford a mixture (3.5:1) of **6** and **7** (0.30 g, 79%) according to GC.

Isopropyl 4*R*-Methyl-2-oxocyclopentan-1-carboxylate (6). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.15 (3H, d, J = 6, CH_3), 1.19 [6H, d, J = 6, $CH(C\underline{H}_3)_2$], 2.22 (5H, m, CH_2, $C\underline{H}CH_3$), 3.26 (1H, t, J = 6.4, $CHCO_2$), 5.35 [1H, septet, J = 6.1, $C\underline{H}(CH_3)_2$].

Isopropyl 5*R*-Methyl-2-oxocyclopentan-1-carboxylate (7). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.19 (3H, d, J = 6, CH_3), 1.19 [6H, d, J = 6, $CH(C\underline{H}_3)_2$], 1.46 and 2.15 (4H, both m, CH_2), 2.75 (1H, m, $C\underline{H}CH_3$), 3.15 (1H, d, J = 9.1, $C\underline{H}CO_2$), 5.35 [1H, septet, J = 6.1, $C\underline{H}(CH_3)_2$].

3*R*-Methylcyclopentane (8): a) A suspension of Na (0.04 g, 1.9 mg-at) in dry toluene (3 mL) (Ar) was heated to 90°C, treated dropwise with a solution of **5** (0.47 g, 1.9 mmol) in dry toluene (4 mL), boiled for 1 h, diluted with hexane, and filtered through a layer of Al_2O_3 (2 cm) to afford **8** (0.15 g, 81%), $[\alpha]_D^{20}$ +152.5° (*c* 1.20, $CHCl_3$) {$[\alpha]_D^{20}$ +154° (*c* 0.6, MeOH) [6]}. The IR, PMR, and ^{13}C NMR spectra were identical to those published previously [11];

b) A solution of **6** and **7** (0.50 g, 2.5 mmol) in DMSO (21 mL) and H_2O (3 mL) was treated with NaCl (0.70 g, 12 mmol), held at 165° for 2 h, and cooled. The aqueous layer was extracted with petroleum ether, dried over Na_2SO_4, and evaporated to afford **8** (0.16 g, 65%) that was identical to that obtained in a).

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