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MODIFIED SYNTHESIS OF METHYL (1*R*,2*R*,3*E*,5*R*)-3-(HYDROXYIMINO)-5-METHYL-2-(1-METHYLETHYL)-CYCLOHEXANECARBOXYLATE FROM (*R*)-4-MENTHEN-3-ONE

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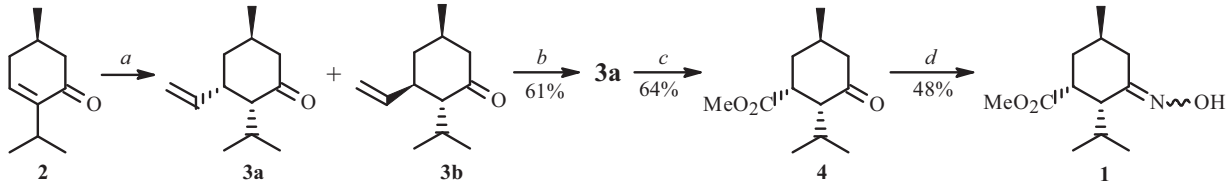
*A modified stereospecific synthesis of potentially biologically and pharmacologically active methyl (1*R*,2*R*,3*E*,5*R*)-3-(hydroxyimino)-5-methyl-2-(1-methylethyl)cyclohexanecarboxylate from (*R*)-4-menthen-3-one was developed using sequential 1,4-conjugate addition of Norman reagent catalyzed by CuI–BF_3·Et_2O–$CuCl_2$ and ozonolysis–reduction of the intermediate (*R,R,R*)-vinylmenthone by hydroxylamine hydrochloride in MeOH.*

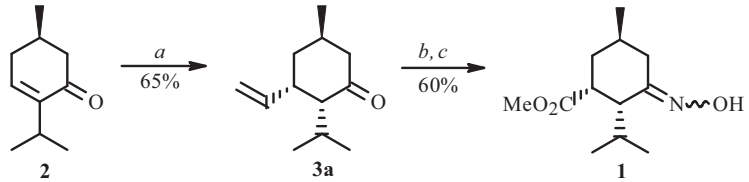
Keywords: (*R*)-4-menthen-3-one, (*R*,*R*,*R*)-vinylmenthone, Norman reagent, ozonolysis–reduction, hydroxylamine hydrochloride, synthesis.

The synthesis of methyl (1*R*,2*R*,3*E*,5*R*)-3-(hydroxyimino)-5-methyl-2-(1-methylethyl)cyclohexanecarboxylate (**1**), a promising chiral synthon with potential pharmacological activity, from (*R*)-4-menthen-3-one (**2**) was reported earlier [1]. The scheme included sequential steps of catalyzed tandem CuI–BF_3·Et_2O 1,4-addition of vinylmagnesiumbromide, chromatographic isolation of (*R*,*R*,*R*)-vinylmenthone (**3a**) from the resulting mixture (18:1) with its stereoisomer (**3b**), ozonolytic conversion in methanolic NaOH into the key ketoester (**4**), and final oximation in 19% overall yield.



a. CH_2=CHMgBr, CuI-BF_3·Et_2O, Et_2O-THF, –78°C; *b*. SiO_2; *c*. O_3/MeOH-CH_2Cl_2, NaOH, –78°C; *d*. NH_2OH·HCl, Py, 20°C

Herein we present a modified synthesis of **1** from the same cycloenone (**2**) that enables it to be obtained in greater yield (39%) and fewer steps. For this, 1,4-conjugate addition of Norman reagent to (*R*)-4-menthen-3-one (**2**) was carried out at –78°C in the presence of the same complex CuI–BF_3·Et_2O with increased polarization of the conjugated enones through interaction of added $CuCl_2$ (1.33 eq) with the carbonyl O atom [2, 3]. This increased the enantioselectivity of the process [4, 5]. As a result, the single stereoisomer (*R*,*R*,*R*)-vinylmenthone (**3a**) was obtained in good yield (65%). Ozonolysis of **3a** and subsequent reduction of the peroxide products with an excess of hydroxylamine hydrochloride gave the desired **1**. According to ^{13}C NMR data, the anti-isomer dominated [*anti-syn* 55:45 from the intensity ratio of *anti*- (57.79) and *syn*- (49.71) C-2 resonances].



a. CH_2=CHMgBr, CuI-BF_3·Et_2O, $CuCl_2$ (1.33 eq.), THF, –78°C; *b*. O_3, MeOH, 0°C; *c*. NH_2OH·HCl, 20°C

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EXPERIMENTAL

IR spectra were recorded on a Prestige-21 IR instrument (Shimadzu) in thin layers. NMR spectra were recorded in $CDCl_3$ on an AM-300 spectrometer (Bruker) at operating frequency 300.13 MHz (^1H) and 75.47 (^{13}C). Resonances of $CD(H)Cl_3$ were used as standards, i.e., impurity protons in the deuterated solvent for PMR (δ 7.27 ppm) and the average $CDCl_3$ resonance (δ 77.00 ppm) for ^{13}C NMR. Resonances were assigned using COSY (H–H) and COSY (C–H) spectra. The H–H SSCC were determined using double resonance. Chromatographic analysis was performed in Chrom-5 [column length 1.2 m; stationary phase, silicone SE-30 (5%) + OV-225 (3%) on Chromaton N-AW-DMCS (0.16–0.20 mm), operating temperature 50–200°C] and GC-9A (Shimadzu) [quartz capillary column, length 25 m, stationary phase DB-1 (0.25 μm), operating temperature 80–280°C] instruments with He carrier gas. Optical rotation was measured on a Perkin–Elmer 241-MC polarimeter. Column chromatography was carried out over silica gel L (60–200 μm) (Lancaster, England). TLC used Sorbfil plates (Krasnodar). Solvents were dried using standard methods. THF was distilled from diisobutylaluminum hydride before use; MeOH, from Na.

(2*R*,3*R*,5*R*)-3-Ethenyl-5-methyl-2-(1-methylethyl)cyclohexanone (3a). A stirred suspension prepared from Mg (1.93 g, 79.2 mg-at) and CH_2=CHBr (8.47 g, 8.74 mL, 79.2 mmol) in anhydrous THF (80 mL, Δ, Ar) was treated with CuI (7.55 g, 39.6 mmol, –30°C, Ar), stirred for 10 min, cooled to –78°C, treated dropwise with $BF_3{\cdot}Et_2O$ (5.62 g, 39.6 mmol), stirred for 5 min, treated with $CuCl_2$ (7.13 g, 52.8 mmol), stirred for 5 min, treated dropwise with **2** (2.00 g, 13.2 mmol) in anhydrous THF (5 mL), stirred for 7 h at –78°C, treated with saturated NH_4Cl solution (10 mL), stirred for 1.5 h, gradually warmed to room temperature, and extracted with Et_2O (3 × 120 mL). The combined extracts were washed with saturated NaCl solution (until pH 7), dried over $MgSO_4$, evaporated, and chromatographed over a column of SiO_2 (petroleum ether eluent) to afford **3a** (1.54 g, 65%), R_f 0.68 (petroleum ether:*t*-BuOMe, 3:1), $[\alpha]_D^{21}$ +4.5° (*c* 3.69, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 3078 (CH_2=CHR), 3015 (CH_2=CHR), 1708 (C=O), 1654 (C=C), 915 (C=C).

PMR spectrum (300.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.73 and 0.82 [6H, d, J = 6.8, $(C\underline{H}_3)_2CH$], 0.91 (3H, d, J = 6.7, $C\underline{H}_3$C-5), 1.59 (1H, ddd, ^2J = 12.0, ^3J = 4.9, ^3J = 9.8, H_a-4), 1.73–1.83 [1H, m, $(CH_3)_2C\underline{H}$], 1.85–1.94 (1H, m, H_e-4), 2.03–2.12 (1H, m, H-5), 2.07 (1H, dd, ^3J = 7.4, ^3J = 5.1, H-2), 2.08 (1H, dd, ^2J = 7.7, ^3J = 12.4, H_a-6), 2.28 (1H, dd, ^2J = 7.7, ^3J = 2.1, H_e-6), 3.03 (1H, ddd, ^3J = 7.4, ^3J = 5.7, ^3J = 4.9, H-3), 4.98 (2H, dd, ^2J = 16.7, ^3J = 11.4, H-2′), 5.52 (1H, ddd, ^2J = 16.7, ^3J = 11.4, ^4J = 5.4, H-1′).

^{13}C NMR spectrum (75.47 MHz, $CDCl_3$, δ, ppm): 20.18 (q, $\underline{C}H_3$C-5), 20.87 and 21.92 [q, $CH(\underline{C}H_3)_2$], 29.53 (d, C-5), 27.94 [d, $\underline{C}H(CH_3)_2$], 34.50 (t, C-4), 40.88 (d, C-3), 47.59 (t, C-6), 60.86 (d, C-2), 116.53 (t, C-2′), 136.87 (d, C-1′), 213.70 (s, C-1).

Methyl (1*R*,2*R*,3*E*,5*R*)-3-(hydroxyimino)-5-methyl-2-(1-methylethyl)cyclohexanecarboxylate (1). An O_3/O_2 mixture (ozonator production 35 mmol O_3/h) was passed through a solution of **3a** (1.20 g, 6.7 mmol) in anhydrous MeOH (30 mL) until the starting compound disappeared (TLC monitoring). The mixture was purged with Ar, cooled to 0°C, treated with $NH_2OH{\cdot}HCl$ (3.26 g, 46.9 mmol), stirred for 48 h at room temperature, and evaporated in vacuo. The solid was treated with Et_2O (300 mL), washed with saturated NaCl solution (until pH 7), dried over $MgSO_4$, and evaporated. The solid was washed with petroleum ether (70 mL) to afford **1** (0.90 g, 60%), R_f 0.42 (petroleum ether:*t*-BuOMe, 2:1). IR spectrum (ν, cm^{-1}): 3260 (O–H), 1738 (C=O), 1654 (C=N), 970 (N–O).

PMR spectrum: 0.89 (3H, d, ^3J = 6.1, CH_3C-5), 0.97 and 1.07 [6H, both d, ^3J = 6.5, $(CH_3)_2$C], 1.41–1.56 (1H, m, H_a-6), 1.95–2.15 (3H, m, H-2, H-5, H_a-4), 2.93–3.00 (1H, m, H-3), 3.00–3.05 (2H, m, H_e-4, 6), 3.65 (3H, s, CH_3O).

^{13}C NMR spectrum: 20.50 (q, $\underline{C}H_3$C-5), 20.91 and 22.44 [q, $(\underline{C}H_3)_2$C], 25.70 (d, H$\underline{C}$C-2), 26.68 (t, C-6), 31.29 (d, C-5), 31.13 (t, C-4), 42.85 (d, C-3), 49.71 (d, C_{syn}-2), 51.38 (q, H_3CO), 51.79 (d, C_{anti}-2), 158.94 (s, C-1), 174.20 (s, O$\underline{C}$C-1).

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