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REACTIONS OF (*R*)-4-MENTHEN-3-ONE WITH ALUMINUM- AND BORON-CONTAINING HYDRIDES

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*It was shown that the most effective and stereospecific hydride reductant for (*R*)-4-menthen-3-one to (1*R*,3*R*)-menthen-3-ol was i-Bu$_2$AlH whereas the complex BH$_3$·THF, which exhibited the same properties relative to the substrate carbonyl, was a regiospecific but relatively non-stereospecific hydroborating reagent of its double bond.*

Keywords: (*R*)-4-menthen-3-one, aluminum- and boron-containing hydride reagents, reduction, hydroboration–oxidation.

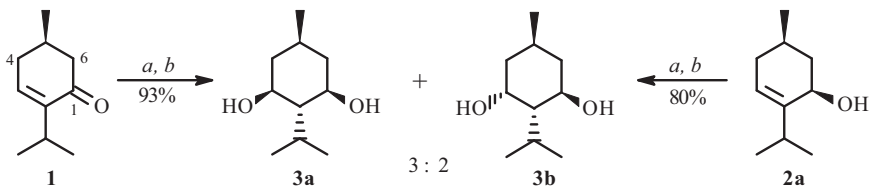
It was shown earlier [1] that reduction of optically pure (*R*)-4-menthen-3-one (**1**), which is available from natural *l*-menthol [2], by $LiAlH_4$ in Et_2O at 0°C occurs with formation of a mixture (93:7) of (1*R*,3*R*)-(**2a**)- and (1*R*,3*S*)-(**2b**)-diastereomeric menthen-3-ols.

We performed a series of experiments in which the Al- ($LiAlH_4$, *i*-Bu_2AlH) and B-containing ($NaBH_4$) hydride reagents; solvents (Et_2O, THF, CH_2Cl_2, EtOH); and temperature conditions (−78, 0, 25°C) were varied. Table 1 presents the experimental results.

The most selective reductant was *i*-Bu_2AlH. A single (1*R*,3*R*)-diastereomer (**2a**) was formed in practically all solvents.

Reaction of cycloenone **1** with the known hydride and hydroborating complex BH_3·THF, which was prepared *in situ* from BF_3·Et_2O and $NaBH_4$ in THF [3, 4], and subsequent oxidation by basic H_2O_2 produced a mixture (3:2 according to GC and NMR) of epimeric (1*R*,3*S*)-(**3a**)- and (1*R*,3*R*)-(**3b**)-5-methyl-2-(1-methylethyl)cyclohexane-1,3-diols. An analogous mixture of epimers (**3a**) and (**3b**) was formed via hydroboration–oxidation of (1*R*,3*R*)-menthen-3-ol (**2a**). This showed that the complex BH_3·THF is a stereospecific hydride reagent for the oxo-group in (*R*)-4-menthen-3-one (**1**) and a regiospecific and slightly stereospecific hydroborating agent for the double bond in it and the product of its hydride reduction (**2a**).

Stereoisomers **3a** and **3b** were identified using PMR and ^{13}C NMR spectroscopy after separating them by chromatography. The spectra were analyzed by comparing them with spectral parameters of various menthol stereoisomers and the similar structural analogs isopropylcyclohexanols and menthone [5, 6].



1 **3a** **3b** **2a**

a. $NaBH_4$, BF_3·OEt_2, THF, 20°C; *b*. NaOH, H_2O_2

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TABLE 1. Dependence of Yield and Ratio of Stereoisomers of (1*R*,3*R*)-(**2a**)- and (1*R*,3*S*)-(**2b**)-Menthen-3-ols According to GC Data on the Nature of the Hydride Reductant of Cycloenone **1**, Solvent, and Temperature (T)

Solvent	T, °C	Yield, %	Ratio **2a**:**2b**, %
		$LiAlH_4$	
THF	–78	86	100:0
Et_2O	–78	83	100:0
THF	0	73	92:8
Et_2O	25	79	87:13
THF	25	76	75:25
		i-Bu_2AlH	
Et_2O	–78	85	100:0
CH_2Cl_2	–78	89	100:0
Et_2O	0	81	100:0
CH_2Cl_2	0	87	100:0
Et_2O	25	79	86:14
CH_2Cl_2	25	91	100:0
		$NaBH_4$	
THF	–78	86	100:0
EtOH	–78	83	100:0
THF	0	79	79:21
EtOH	0	86	91:9
THF	25	89	75:25
EtOH	25	89	80:20

NMR spectra contained resonances of only one diastereomeric pair, *meso*-(**3a**) and *dl*-(**3b**). Chemical shifts in ^{13}C spectra and SSCC of methine protons at the hydroxyls (^3J = 10.6 Hz of the triplet and 4.2 Hz of the doublet component) indicated that all four substituents of the symmetric *meso*-isomer (**3a**) had the equatorial orientation. The difference of chemical shifts in ^{13}C spectra and SSCC of methine protons at the hydroxyls (H_a 4.25, dt, ^3J = 4.1 and 9.9 Hz; H_e 4.12, dt, ^3J = 4.9 and 3.1 Hz) in addition to the resonance at stronger field for C-2 (51.70 ppm) indicated that one of the hydroxyls of the *dl*-isomer (**3b**) had the axial orientation. The spectral parameters of the Me- and *i*-Pr-substituents were similar in *l*-menthol and agreed with their equatorial orientation in both stereoisomeric diols (**3a** and **3b**).

EXPERIMENTAL

IR spectra were recorded in a thin layer on an IR Prestige-21 instrument (Shimadzu). NMR spectra were taken in $CDCl_3$ with TMS internal standard on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for PMR and 75.47 MHz for ^{13}C NMR). PMR and ^{13}C NMR spectra were analyzed and resonances were assigned using 2D homonuclear COSY (H–H) correlation spectroscopy. Chromatography was performed on a GC-9A chromatograph (Shimadzu) (quartz capillary column, 25 m, OV-101 stationary phase, 80–260°C operating temperature), He carrier gas. Column chromatography was carried out over silica gel L (60–200 μm) (Russia); TLC, on Sorbfil plates (Russia). Petroleum ether (PE, bp 40–70°C) was used for chromatography. Solvents were dried by standard methods.

Reduction of (*R*)-4-Menthen-3-one (1) by $LiAlH_4$. a) A suspension of $LiAlH_4$ (0.15 g, 3.8 mmol) in anhydrous Et_2O (25 mL) was stirred (−78 or 25°C, Ar), treated with enone **1** (0.30 g, 2.0 mmol), stirred for 2 h, treated dropwise at these same temperatures with H_2SO_4 solution (4 mL, 0.1 N), and stirred for 0.5 h. The organic layer was separated. The isolated precipitate was washed with *t*-BuOMe (3 × 5 mL) on a Schott filter. The combined organic extract was washed with saturated NaCl solution (2 × 5 mL), dried over Na_2SO_4, and evaporated. The residue was analyzed by capillary GC.

b) A suspension of $LiAlH_4$ (0.15 g, 3.8 mmol) in anhydrous THF (25 mL) was stirred (−78, 0, or 25°C, Ar), treated with **1** (0.30 g, 2.0 mmol), stirred for 2 h, treated dropwise at these same temperatures with H_2SO_4 (4 mL, 0.1 N), and stirred for 0.5 h. The mixture was passed through a Schott filter. The filtrate was evaporated. The residue was diluted with *t*-BuOMe (50 mL), washed with saturated NaCl solution (2 × 5 mL), dried over Na_2SO_4, and evaporated. The residue was analyzed by capillary GC.

Reduction of (*R*)-4-Menthen-3-one (1) by *i*-Bu_2AlH. c) A solution of enone **1** (0.50 g, 3.3 mmol) in anhydrous CH_2Cl_2 or Et_2O (50 mL) was treated dropwise (−78, 0, or 25°C, Ar) with a solution of *i*-Bu_2AlH (1.6 mL, 73%) in toluene, stirred for 2 h, treated at these same temperatures with cold H_2O (7 mL), and stirred for 0.5 h. The resulting precipitate was

filtered off through a layer of Al_2O_3 (5 cm). The organic layer was dried over Na_2SO_4 and evaporated. The residue was analyzed by capillary GC.

Reduction of (*R*)-4-Menthen-3-one (1) by $NaBH_4$. d) A suspension of $NaBH_4$ (0.15 g, 3.8 mmol) in anhydrous EtOH or THF (25 mL) was stirred, treated (−78, 0, or 25°C, Ar) with enone **1** (0.30 g, 2.0 mmol), stirred for 2 h, treated dropwise at these same temperatures with H_2O (4 mL), stirred for 0.5 h, and passed through a Schott filter. The filtrate was evaporated. The residue was diluted with *t*-BuOMe (50 mL), washed with saturated NaCl solution (2 × 5 mL), dried over Na_2SO_4, and evaporated. The residue was analyzed by capillary GC.

(1*R*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohex-2-en-1-ol (2a). $[\alpha]_D^{20}$ −31.5°(*c* 0.6, EtOH), $[\alpha]_D^{24}$ −32.0° (*c* 1.0, EtOH), R_f 0.55 (PE:*t*-BuOMe, 2:1). IR spectrum (KBr, ν, cm^{-1}): 1664 (C=C), 3048–3600 (O–H). PMR spectrum (300.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.82 (3H, d, J = 7.0, 5-CH_3), 1.15 [3H, d, J = 6.7, CH(C$\underline{H}_3$)$_2$], 1.19 [3H, d, J = 6.7, CH(C$\underline{H}_3$)$_2$], 1.52 (1H, ddd, ^{2}J = 11.3, ^{3}J = 8.4, ^{3}J = 2.0, H_a-6), 1.62–1.70 (1H, m, H_e-6), 1.62–1.75 (1H, m, H_a-4), 1.98–2.06 (1H, m, H-5), 2.18–2.20 (1H, m, H_e-4), 2.95 [1H, d, J = 6.7, C$\underline{H}$(CH$_3$)$_2$], 4.57 (1H, dd, ^{2}J = 5.4, ^{3}J = 5.3, H_a-1), 4.80 (1H, br.s, OH), 5.48 (1H, dd, ^{2}J = 5.4, ^{3}J = 4.7, H-3).

^{13}C NMR spectrum (75.47 MHz, $CDCl_3$, δ, ppm): 20.77 (q, 5-CH_3), 21.80 [q, CH(C$\underline{H}_3$)$_2$], 22.58 [q, CH(C$\underline{H}_3$)$_2$], 29.16 (d, C-5), 29.18 [d, C$\underline{H}$(CH$_3$)$_2$], 34.25 (t, C-4), 42.25 (t, C-6), 67.53 (d, C-1), 120.26 (d, C-3), 145.89 (s, C-2).

Hydroboration-Oxidation of (*R*)-4-Menthen-3-one (1). A suspension of **1** (0.70 g, 4.6 mmol) and $NaBH_4$ (0.63 g, 16.6 mmol) in anhydrous THF (40 mL) under Ar at 20°C was treated dropwise with a solution of $BF_3{\cdot}Et_2O$ (0.8 mL) in anhydrous THF (15 mL), stirred for 3.5 h at 20°C, treated dropwise with H_2O (1.5 mL), stirred for 10 min, treated sequentially with NaOH solution (1.6 mL, 3 N) and H_2O_2 (1.6 mL, 30%), stirred for 16 h, diluted with *t*-BuOMe (70 mL), washed with saturated NaCl solution (2 × 5 mL), dried over Na_2SO_4, and evaporated to afford a mixture (3:2) of diastereomeric diols **3a** and **3b** (0.73 g, 93%) that were separated by column chromatography (SiO_2, PE→PE:EtOAc (5:1)→EtOAc).

Hydroboration-Oxidation of (1*R*,3*R*)-menthen-3-ol (2a). A suspension of **2a** (0.70 g, 4.5 mmol) and $NaBH_4$ (0.62 g, 17.5 mmol) in anhydrous THF (40 mL) under Ar at 20°C was treated dropwise with a solution of $BF_3{\cdot}Et_2O$ (0.8 mL) in anhydrous THF (15 mL), stirred for 3.5 h at 20°C, treated dropwise with H_2O (1.5 mL), stirred for 10 min, treated with NaOH solution (1.6 mL, 3 N) and H_2O_2 (1.6 mL, 30%), stirred for 16 h, diluted with *t*-BuOMe (70 mL), washed with saturated NaCl solution (2 × 5 mL), dried over Na_2SO_4, and evaporated to afford a mixture (3:2) of diastereomeric diols **3a** and **3b** (0.63 g, 80%) that were separated by column chromatography (SiO_2, PE→PE:EtOAc (5:1)→EtOAc).

(1*R*,3*S*)-5-Methyl-2-(1-methylethyl)cyclohexane-1,3-diol (3a). R_f 0.35 (PE:EtOAc, 2:1). PMR spectrum (300.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.09 [6H, d, J = 7.2, CH(C$\underline{H}_3$)$_2$], 1.13 (3H, d, J = 6.9, 5-CH_3), 1.25–1.60 (4H, m, 2H-4, 2H-6), 1.80–1.95 (2H, br.s, 2OH), 1.91 (1H, dd, ^{2}J = 3.4, ^{3}J = 10.6, H_a-2), 1.93–2.02 (1H, m, H_a-5), 2.23–2.38 [1H, m, C$\underline{H}$(CH$_3$)$_2$], 3.41 (2H, dt, ^{2}J = 10.6, ^{3}J = 4.2, H_a-3, H_a-1).

^{13}C NMR spectrum (75.47 MHz, $CDCl_3$, δ, ppm): 21.62 [q, 2 × (C$\underline{H}_3$)-*i*-Pr], 25.31 (q, 5-CH_3), 26.00 (d, C-5), 27.17 [d, C$\underline{H}$(CH$_3$)$_2$], 44.36 (d, C-4, C-6), 56.67 (d, C-2), 69.88 (d, C-1, C-3).

(1*R*,3*R*)-5-Methyl-2-(1-methylethyl)cyclohexane-1,3-diol (3b). $[\alpha]_D^{20}$ −1.2° (*c* 1.6, CH_2Cl_2), R_f 0.25 (PE:EtOAc, 2:1). PMR spectrum (300.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.94 (3H, d, J = 6.9, 5-CH_3), 0.96 [3H, d, J = 6.5, CH(C$\underline{H}_3$)$_2$], 1.02 [3H, d, J = 6.5, CH(C$\underline{H}_3$)$_2$], 1.22–1.37 (1H, m, H_a-6), 1.37–1.52 (1H, m, H_a-4), 1.60–1.72 (1H, m, H_a-2), 1.69 (1H, dt, ^{2}J = 12.9, ^{3}J = 4.9, H_e-4), 1.80–1.95 (2H, br.s, 2OH), 1.85–1.95 (1H, m, H_e-6), 1.90–2.00 (1H, m, H_a-5), 2.05–2.16 [1H, m, C$\underline{H}$(CH$_3$)$_2$], 4.12 (1H, dt, ^{2}J = 4.9, ^{3}J = 3.1, H_e-1), 4.25 (1H, dt, ^{2}J = 9.9, ^{3}J = 4.1, H_a-3).

^{13}C NMR spectrum (75.47 MHz, $CDCl_3$, δ, ppm): 20.20 [q, 2×(C$\underline{H}_3$)-*i*-Pr], 21.91 (q, 5-CH_3), 25.01 [d, C$\underline{H}$(CH$_3$)$_2$], 25.31 (d, C-5), 37.62 (t, C-6), 38.70 (t, C-4), 51.70 (d, C-2), 68.68 (d, C-3), 69.63 (d, C-1).

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