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LOW-TEMPERATURE HYDRIDE REDUCTION OF (3*R*)-CARVOMENTHOLACTONE

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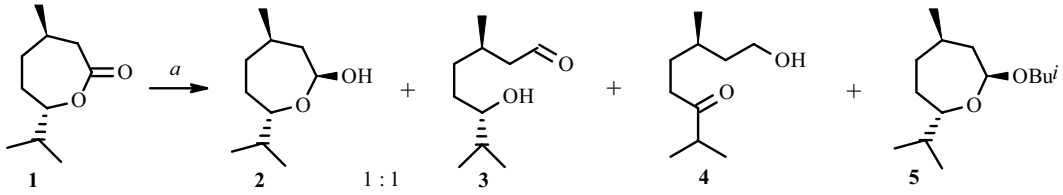
*Low-temperature (–70°C) reduction of (3*R*)-carvomentholactone by diisobutylaluminum hydride in methylenechloride was studied.*

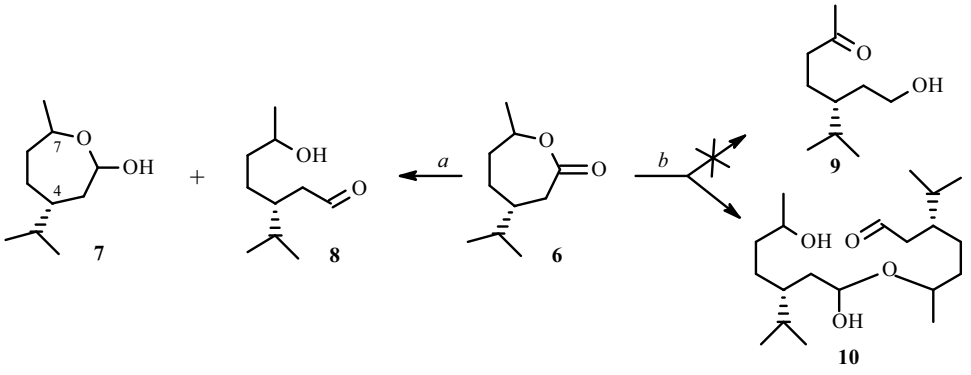
Keywords: (3*R*)-carvomentholactone, diisobutylaluminum hydride (DIBAH), methylenechloride, low-temperature reduction.

We established earlier [1, 2] that low-temperature (–70°C) reduction of (3*R*,6*S*)-mentholactone (**1**) by DIBAH in methylenechloride (CH_2Cl_2) occurred with formation of mentholactol [as a 1:1 mixture of 7*S*-methyl-2*S*-oxepanol (**2**) and 6*S*-hydroxy-3*R*,7-dimethyloctanal (**3**)], hydroxyketone **4**, and 2*S*-isobutyl acetal of mentholactol (**5**). The conditions for preferential formation of each of these were found.



a. 1. Bu^i_2AlH, CH_2Cl_2, –70°C, 2. H_2O

We supposed that (3*R*,6*RS*)-carvomentholactone (**6**), which is isomeric to (3*R*,6*S*)-mentholactone (**1**) and accessible from *R*-(–)-carvone by the literature method [3], would behave similarly under analogous conditions.



a. 1. Bu^i_2AlH, CH_2Cl_2, –70°C, 2. H_2O, 0°C, 83%; *b*. 1. Bu^i_2AlH, CH_2Cl_2, –70°C, 2. H_2O, 10 eq., –60°C, 85%

In fact, it turned out that carvomentholactol (**7**) and its opened form **8** were obtained upon addition by titration at –70°C of an equimolar amount of DIBAH and rapid decomposition of the resulting aluminate by a large excess of water at 0°C.

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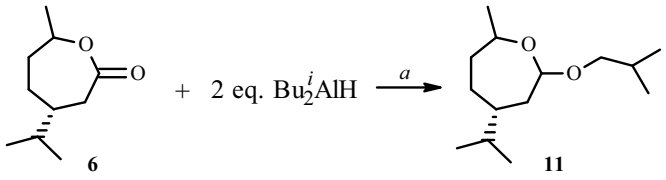
Low-temperature (–70°C) decomposition of the aluminate of carvomentholactol obtained by the method described above with a small excess (up to 10 equiv.) of water and storage of this mixture for 1 h at –50 to –60°C produced, unexpectedly, not the hydroxyketone (**9**) but the dimeric hemiacetal (**10**). The structure of dimeric hemiacetal **10** was proved convincingly by PMR spectra using the ratio (1:1) of intensities of resonances for the hemiacetal (4.78 ppm) and aldehyde (9.71) protons. This indicated unambiguously that the linear dimer had formed. This ratio would have been 2:1 for the trimer; 3:1, for the tetramer, etc.

The expected isobutyl derivative of carvomentholactol (**11**) was obtained via a new reaction in the chemistry of organoaluminum compounds by the action of two and more equivalents of DIBAH on **6** and storage of the reaction mixture for 2 h. It is noteworthy that replacing CH_2Cl_2 by THF or toluene and carrying out the reaction under conditions for formation of isobutyl acetal **11** using two and more equivalents of DIBAH occurred trivally to form the carbomentholactol (**7**, **8**).



6 **11**

a. 1. CH_2Cl_2, –70°C, 2. H_2O, 80%

EXPERIMENTAL

NMR spectra were recorded on a Bruker AM 300 spectrometer [operating frequency 300 (^{1}H) and 75.47 (^{13}C) MHz]. Resonances in NMR spectra were assigned and SSCC were determined using two-dimensional COSY (C–H) and COSY (H–H) correlation spectroscopy and double resonance. ^{13}C NMR spectra were recorded with broad-band proton decoupling in JMOD mode. The internal standard was TMS. Chromatographic analysis was performed on a Shimadzu GC-2014 instrument [DB-35MS (0.20 mm) column, operating temperature 50–360°C] with He carrier gas. Column chromatography was carried out over silica gel (Lancaster, 60–200 μm). TLC analysis was performed on Sorbfil UV-254 plates (Krasnodar) with elution by petroleum ether (PE):EtOAc (1:1). Elemental analyses of all compounds agreed with those calculated. (3*R*,6*RS*)-Carvomentholactone (**6**) was prepared from *R*-(–)-carvone by the literature method [3].

4*R*-Isopropyl-7-methyloxepan-2-ol (7) and 6-Hydroxy-3*R*-isopropylheptanal (8). a) A solution of lactone **6** (2.00 g, 11.8 mmol) in dry CH_2Cl_2 (40 mL) (Ar, –70°C) was treated dropwise with a solution of DIBAH (3.0 mL, 12.0 mmol, 73%) in toluene. After the starting lactone was consumed (15 min, TLC monitoring), the reaction mixture was treated with a mixture of THF (3 mL) and H_2O (10 mL) at ≤–60°C. Then, the mixture was poured into ice (10 mL), diluted with CH_2Cl_2 (50 mL), filtered through a layer of Al_2O_3 (5 cm), rinsing with CH_2Cl_2. The filtrate was dried over Na_2SO_4 and evaporated. The solid was chromatographed (SiO_2, PE:EtOAc eluent, 7:3) to afford a mixture (3:7 according to PMR spectra) of **7** and **8** (1.60 g, 78%).

b) A solution of DIBAH (6.0 mL, 24.0 mmol, 73%) in toluene and anhydrous toluene (or THF) (20 mL) (Ar, –70°C) was treated dropwise with lactone **6** (2.00 g, 11.8 mmol) in anhydrous toluene (or THF) (20 mL), held at –70°C for 2 h, and treated at the same temperature with a mixture of THF (10 mL) and H_2O (10 mL). Then, the reaction mixture was warmed to room temperature, diluted with CH_2Cl_2 (50 mL), filtered through a layer of Al_2O_3 (5 cm), dried over Na_2SO_4, and evaporated to afford an analogous mixture of **7** and **8** (1.78 g, 88%) (in THF, 1.73 g, 85%).

4*R*-Isopropyl-7-methyloxepan-2-ol (7). R_f 0.41 (PE:EtOAc, 7:3).

PMR spectrum ($CDCl_3$, δ, ppm, *J*/Hz, from the mixture with **8**): 0.80 and 0.82 [6H, both d, J = 6.5, $(C\underline{H}_3)_2CH$-4], 1.15 [1.10] (3H, d, J = 6.6, CH_3-7), 1.15–1.23 (1H, m, H-5a), 1.35–1.47 (1H, m, H-3a), 1.38–1.45 (1H, m, H-5b), 1.49–1.52 (1H, m, H-6a), 1.70–1.81 (1H, m, H-3b), 1.70–1.87 (1H, m, H-4), 1.71–1.79 (1H, m, H-6b), 1.75–1.83 [1H, m, $(CH_3)_2C\underline{H}$-4], 3.88–3.95 [3.72-3.81] (1H, m, H-7), 4.75 [4.83] (1H, dd, J = 9.4, 5.5 [8.1, 5.0], H-2).

^{13}C NMR spectrum ($CDCl_3$, from the mixture with **8**): 18.37 [18.74] and 18.94 [19.37] [both q, $(\underline{C}H_3)_2CH$-4], 23.07 [20.44] (q, CH_3-7), 28.41 [27.98] [d, $(CH_3)_2\underline{C}H$-4], 32.74 [30.64] (t, C-5), 36.60 [35.23] (t, C-6), 38.09 [37.65] (t, C-3), 38.44 [42.02] (d, C-4), 66.52 [70.33] (d, C-7), 95.31 [97.02] (d, C-2).

6-Hydroxy-3*R*-isopropylheptanal (8). R_f 0.20 (PE:EtOAc, 7:3).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz, from the mixture with **7**): 0.80 and 0.83 [6H, both d, J = 6.5, $(C\underline{H}_3)_2CH$-3], 1.05 [1.10] (3H, d, J = 6.6, H-7), 1.31–1.44 (1H, m, H-4a), 1.46–1.57 (1H, m, H-4b), 1.60–1.65 (1H, m, H-3), 1.65–1.72 (1H, m, H-5a), 1.80–1.87 [1H, m, $(CH_3)_2C\underline{H}$-3], 2.15–2.20 (1H, m, H-5b), 2.23 (1H, ddd, J = 17.4, 6.0, 2.3, H-2a), 2.36 (1H, ddd, J = 17.4, 6.9, 2.3, H-2b), 3.50 (1H, br.s, OH), 3.90–4.0 [3.63–3.72] (1H, m, H-6), 9.72 (1H, t, J = 2.3, H-1).

^{13}C NMR spectrum ($CDCl_3$, from the mixture with **7**): 18.29 [18.25] and 19.12 [19.66] [both q, $(\underline{C}H_3)_2CH$-3], 23.21 [21.48] (q, C-7), 27.89 [29.78] [d, $(CH_3)_2\underline{C}H$-4], 30.09 [29.78] (t, C-4), 38.06 [38.53] (t, C-5), 38.79 [38.44] (d, C-3), 45.52 [45.43] (t, C-2), 70.18 [72.02] (d, C-6), 203.31 [203.16] (d, C-1).

6{[1,6-Dihydroxy-3*R*-isopropylheptyl]-oxy}-3*R*-isopropylheptanal (10). A solution of lactone **6** (2.00 g, 11.8 mmol) in dry CH_2Cl_2 (40 mL) (Ar, –70°C) was treated dropwise with a solution of DIBAH (3.0 mL, 12.0 mmol, 73%) in toluene, held at that temperature for 1 h, treated at –65°C with a mixture of THF (10 mL) and H_2O (3 mL), and stirred at that same temperature for 1 h. The mixture was warmed to room temperature, diluted with CH_2Cl_2 (50 mL), filtered through a layer of Al_2O_3 (5 cm), rinsing with CH_2Cl_2. The filtrate was dried over Na_2SO_4 and evaporated to afford **10** (1.6 g, 80%).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.75–0.85 [12H, both d, J = 6.8, $(C\underline{H}_3)_2CH$-3, $(C\underline{H}_3)_2CH$-3′], 0.95 (3H, d, J = 6.2, CH_3-7), 1.08 [1.12] (3H, d, J = 6.2, H-7′), 1.28–1.37 (2H, m, H-4a, H-4a′), 1.30–1.37 (1H, m, H-2′a), 1.45–1.52 (1H, m, H-2′b), 1.60–1.68 (2H, m, H-4b, H-4′b), 1.68–1.74 [4H, m, H-3, H-3′, $(CH_3)_2C\underline{H}$-3, $(CH_3)_2C\underline{H}$-3′], 1.72–1.80 (1H, m, H-5a), 1.79–1.84 (1H, m, H-5′a), 2.21 (1H, ddd, J = 16.8, 6.4, 5.2, H-2a), 2.30–2.33 (1H, m, H-5b), 2.32 (1H, ddd, J = 16.8, 6.4, 5.2, H-2b), 2.36–2.43 (1H, m, H-5′b), 3.6 (2H, br.s, HO-6, HO-1), 3.68–3.74 (1H, m, H-6), 4.31–4.43 (1H, m, H-6′), 4.78 [5.07] (1H, dd, J = 9.0, 5.6 [9.1, 5.4], H-1′), 9.71 (1H, dd, J = 6.4, 5.6, H-1).

^{13}C NMR spectrum ($CDCl_3$): 18.13, 19.55 [both q, $(\underline{C}H_3)_2CH$-3], 18.39, 19.06 [both q, $(\underline{C}H_3)_2CH$-3′], 23.24 [22.12] (q, C-7), 23.30 [22.40] (q, C-7′), 26.88 (t, C-4), 27.49 (t, C-4′), 28.99 [29.22] [d, $(CH_3)_2\underline{C}H$-3], 29.48 [29.37] [d, $(CH_3)_2\underline{C}H$-3′], 33.41 [33.73] (d, C-3′), 37.97 [38.44] (t, C-5′), 38.21 [38.73] (t, C-5), 38.29 [37.97] (t, C-2′), 38.44 (d, C-3), 45.30 (t, C-2), 67.72 [67.90] (d, C-6), 70.42 [70.98] (d, C-6′), 99.39 [99.27] (d, C-1′), 203.35 (d, C-1).

2-Isobutoxy-4*R*-isopropyl-7-methyloxepane (11). A solution of DIBAH (6.0 mL, 24.0 mmol, 73%) in toluene and dry CH_2Cl_2 (20 mL) (Ar, –70°C) was treated dropwise with lactone **6** (2.00 g, 11.8 mmol) in dry CH_2Cl_2 (20 mL), held at –70°C for 2 h, and treated at that same temperature with a mixture of THF (10 mL) and H_2O (10 mL). The mixture was warmed to room temperature, diluted with CH_2Cl_2 (50 mL), filtered through a layer of Al_2O_3 (5 cm), dried over Na_2SO_4, and evaporated. The solid was chromatographed (SiO_2, PE) to afford **11** (2.15 g, 80%), R_f 0.60 (PE:EtOAc, 5:1).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.75 (3H, d, J = 6.5, H-3′), 0.77 and 0.86 [6H, both d, J = 6.7, $(C\underline{H}_3)_2CH$-4], 0.83 (3H, d, J = 6.5, CH_3-2′), 1.08 [1.09] (3H, d, J = 6.7, CH_3-7), 1.12–1.19 (1H, m, H-5a), 1.24–1.32 (1H, m, H-6a), 1.30–1.37 (1H, m, H-4), 1.36–1.41 (1H, m, H-3a), 1.50–1.61 (1H, m, H-5b), 1.55–1.64 (1H, m, H-6b), 1.55–1.63 [1H, m, $(CH_3)_2C\underline{H}$-4], 1.75–1.84 (1H, m, H-3b), 1.75–1.84 (1H, m, H-2′), 3.10 [3.09] (1H, dd, J = 9.6, 6.3 [6.2], H-1′a), 3.39 [3.37] (1H, dd, J = 9.4, 7.2 [9.1, 7.3], H-1′b), 3.84–3.90 (1H, m, H-7), 4.58 [4.72] (1H, dd, J = 9.07, 5.48 [7.9, 7.7], H-2).

^{13}C NMR spectrum ($CDCl_3$): 18.22 (q, C-3′), 18.76 (q, CH_3-2′), 19.28, 19.40 [both q, $(\underline{C}H_3)_2CH$-4], 23.01 [20.47] (q, CH_3-7), 28.38 [27.99] [d, $(CH_3)_2\underline{C}H$-4], 32.75 [30.61] (t, C-5), 33.87 [33.15] (d, C-2′), 36.53 [33.99] (t, C-6), 38.58 [40.17] (d, C-4), 39.73 [37.37] (t, C-3), 66.08 [66.46] (d, C-7), 73.82 [74.72] (t, C-1′), 100.57 [98.84] (d, C-2).

REFERENCES

1. G. Yu. Ishmuratov, M. P. Yakovleva, V. A. Vydrina, E. F. Khasanova, R. R. Muslukhov, N. M. Ishmuratova, and G. A. Tolstikov, *Khim. Rastit. Syr′ya*, 23 (2007).
2. G. Yu. Ishmuratov, V. A. Vydrina, M. P. Yakovleva, E. F. Valeeva, R. R. Muslukhov, and G. A. Tolstikov, *Zh. Org. Khim.*, **47**, 471 (2011).
3. P. Goswami, S. Hazarika, A. M. Das, and P. Chowdhuri, *Indian J. Chem. Sec. B*, **43**, 1275 (2004).