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Oxidation of (1*S*,5*R*,7*R*,*S*)-(4,7-Dimethyl-6-oxabicyclo[3.2.1]oct-3-en-7-yl) methanol with Pyridinium Chlorochromate

S. A. Torosyan, F. A. Gimalova, R. F. Valeev, and M. S. Miftakhov

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences
Ufa, 450054 Russia; e-mail: bioreg@anrb.ru

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Abstract—The oxidation of (1*S*,5*R*,7*R*,*S*)-(4,7-dimethyl-6-oxabicyclo[3.2.1]oct-3-en-7-yl)methanol epimeric at the C^7 atom resulted in scalemic (5*R*)-5-acetyl-2-methylcyclohex-2-en-1-one.

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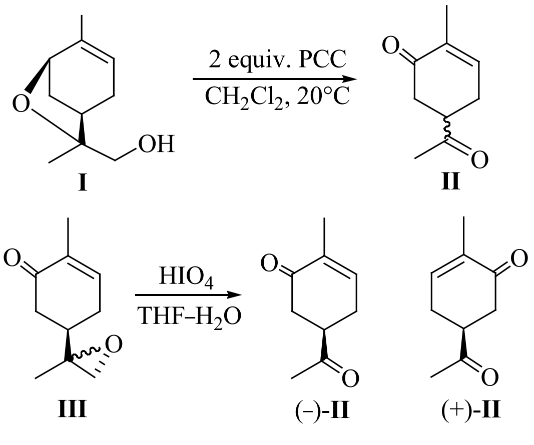
Corey's reagent $C_5H_6N^+CrO_3Cl^-$ (pyridinium chlorochromate, PCC) [1] is a stable and convenient for handling oxidant for alcohols, series of S-, N-, B-containing compounds, for activated C–H and C=C bonds [2]. Among the synthetically valuable PCC applications the oxidation of allyl alcohols should be mentioned providing rearranged α,β-unsaturated aldehydes and ketones [3, 4]. We observed an interesting example of involvement into similar succession of conversions in the course of the study of oxidation with PCC of a mixture of alcohol **I** epimeric at C^7-atom (~6 : 5) and containing an allylether fragment. As a result of this reaction we obtained in a good yield cyclohexenone **II** with $[\alpha]_D^{20}$ –2.5° (*C* 0.09, MeOH) (Scheme 1). The rotation angle of the sample (–)-(**II**) obtained by the splitting of the epoxide **III** with periodic acid proved to be –53.0° (*C* 0.26, MeOH). The difference in the rotation angles of the samples of cyclohexenone **II** from two experiments on the oxidation of alcohol **I** with PCC showed the materially total loss of the opical activity in the course of oxidation, consequently, on the formation of commeasurable amounts of (–)- and (+)-diketone **II**.

PCC is known to be of weakly acidic character. The R-(–)carvone derivatives with the C^4-acetyl function resembling compound **II** are not prone to epimerization in the H^+-containing environment [5, 6]. Therefore the epimerization at the center C^5 of diketone **II** under the conditions of oxidation of alcohol **I** with PCC is ruled out. We presume that the formation of approximately equal amounts of (–)- and (+)-enantiomers of diketone **II** is due to the streochemical heterogeneity of compound **I** governing different directions of the oxidative splitting with pyridinium chlorochromate.

Inasmuch as alcohol **I** used in the study was a mixture of 7*S*- and 7*R*-hydroxymethyl-epimers in the ratio ~6 : 5, the necessary condition of the essential racemiza-

Scheme 1.

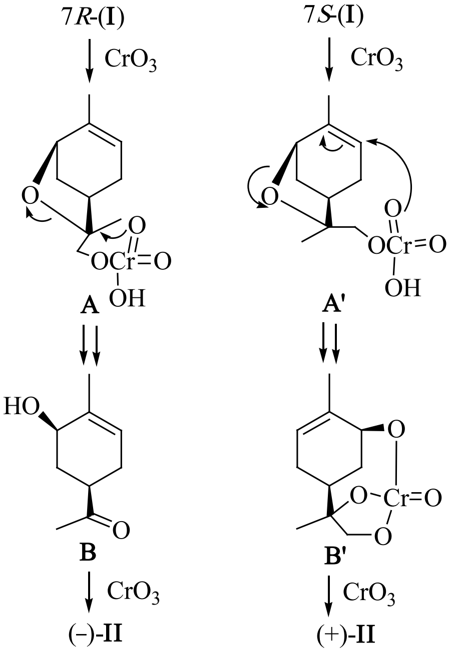


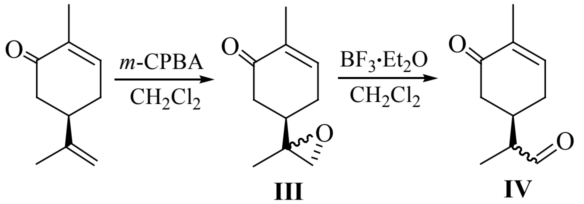
tion should be the process where each of these epimers would react with PCC giving a single enantiomer. This statement is made clear by the possible versions of the successive transformations of alcohol **I** epimers shown in Scheme 2. In keeping with the common concepts on the oxidation with chromates [7] similar intermediates **A** and **A'** are generated in the first stage. In the first case the oxidative fragmentation of **A** initiated by PCC occurs through intermediate **B** [8] and results in diketone (–)-(**II**). In intermediate **A'** owing to the favorable spatial orientation of the Cr=O bond the substitution of S_N2' type in the allyl-ether fragment gets probable. Intermediate **B'** formed in this process suffers the fragmentation into ketone (+)-(**II**).

Thus by the example of oxidation of alcohol **I** we demonstrated new versions of transformations initiated by PCC, including the oxidation in the tertiary allyl site of the substrate along the "1,3-transition" pathway and fragmentation in the quaternary center containing a hydroxymethyl group with the generation of a keto function.

Alcohol **I** used in the study was synthesized from R-(–)-carvone. First epoxide **III** was obtained by the reaction with *m*-CPBA (3-chloroperoxybenzoic acid) in CH_2Cl_2 at 20°C. This reaction is exclusively regioselective but not stereoselective. Epoxide **III** is an epimer mixture in the ratio ~6 : 5 with respect to the epoxy-bearing center. At its purification on silica gel insignificant amounts of aldehyde **IV** were found. The same compound was obtained in high yield at keeping epoxide **III** in CH_2Cl_2 in the presence of $BF_3·Et_2O$.

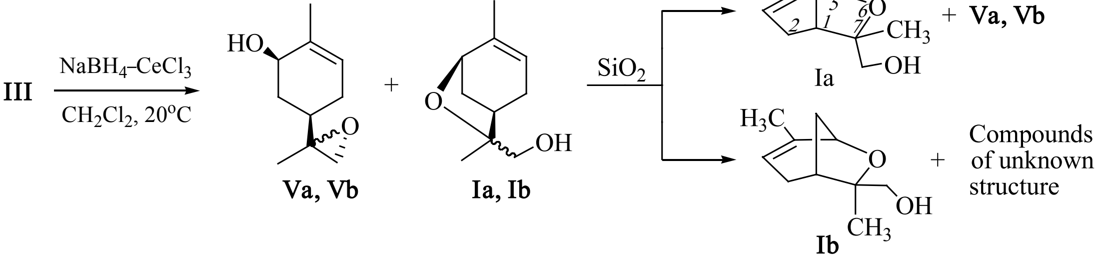
Scheme 2.





The reduction of epoxyketone **III** by the system $NaBH_4–CeCl_3$ in MeOH at 20°C was carried out till complete consumption of compound **III** (TLC monitoring) (Scheme 3). Like in similar processes [6], the stereochemical result of the reduction of epoxide **III** was governed by the steric control of C^5-substituent: The predominant formation of β-alcohol **Va** was observed. However this reaction was complicated by the simultaneous opening of the epoxide by the alkoxy anion in alcohol **Va** resulting in bicycle **I**. As a result formed a mixture of epoxy- (**V**) and bicyclic (**I**) alcohols in the ratio 2 : 1 and in overall yield 80%. This mixture by repeated chromatography on SiO_2 was separated in two fractions of different polarity.

Scheme 3.



Therewith the good separation of bicycle **I** diastereomers was attained, but each diastereomer contained a minor side product. The less polar fraction was composed of the mixture of β-epoxyalcohol **Va,Vb** and diastereomer **Ia**, ~1 : 1, and the more polar fraction was the mixture of diastereomer **Ib** and compound of unidentified structure in the ratio 3 : 1. The characteristic signals in the ^{1}H NMR spectra used for the assignment of diastereomers **Ia, Ib** are the peaks of the protons of the methyl groups in the position *7* and of CH_2O respectively: Due to the steric hindrances they are located more upfield.

Hence the products of this reaction are isomer pairs of compounds **V** and **I** with a little prevalence of bicycle **I**. It was formerly [9] indicated the possibility of formation of epimeric mixture **Ia, Ib** at the reduction of epoxyketone **III** with Luche reagent.

Then the mixture of compounds **V** and **I** was subjected to silylation in the system TBSCl–Im in CH_2Cl_2 [10]. Therewith virtually complete conversion was observed of the components of this mixture into *tert*-butyldimethylsilyl-protected (TBS) derivative **VI**, and the inherent to epoxide **III** epimeric composition (6 : 5) was conserved in TBS-ether **VI**. Finally the removal of the protective group in ether **VI** by the fluoride ion led to the formation of bicyclic alcohol **I** used in the study also as a mixture of epimers.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Shimadzu IR Prestige-21 from thin films. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequencies 300.13 and 75.47 MHz respectively in $CDCl_3$, internal reference TMS. The rotation angles were measured on an instrument Perkin Elmer-341. Mass spectra were taken on an instrument Thermo Finnigan MAT 95XP, ionizing energy 70 eV, temperature of ionizing chamber 200°C, that of sample admission, 5–270°C, heating rate 22 deg/min. The reaction progress was monitored on Sorbfil plates, development with a solution of anise aldehyde and sulfuric acid in ethanol with subsequent heating to 120–150°C. The products of the synthesis were isolated by column chromatography on silica gel (30–60 g of sorbent per 1 g of substance), as eluents freshly distilled solvents were used.

(1*S*,5*R*,7*R*,*S*)-(4,7-Dimethyl-6-oxabicyclo[3.2.1]-oct-3-en-7-yl)methanol (Ia, Ib). To the stirred solution of 0.12 g (0.43 mmol) of silyl ether **VI** in 6 ml of anhydrous THF was added by portions 0.16 g (0.51 mmol) of *H*-$Bu_4N^+F^-$, the reaction mixture was stirred at room temperature till complete consumption of the initial compound (TLC monitoring). The residue after the evaporation in a vacuum was purified by column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 1). Yield 0.05 g (85%), isomers mixture. IR spectrum, cm^{-1}: 3414, 2960, 2927, 2873, 1700, 1629, 1448, 1410, 1375, 1159, 1130, 1099, 1070, 1032, 991, 914, 829, 756. Mass spectrum, *m/z* (I_{rel}, %): 168 $[M]^+$ (1), 137 $[M-CH_2OH]^+$ (90), 93 (100), 43 $[CH_3CO]^+$ (98). Found, %: C 71.97; H 9.77. M^+ 168.10. $C_{10}H_{16}O_2$. Calculated, %: C 71.39; H 9.59. *M* 168.23.

Oxidation of compound I with pyridinium chlorochromate. To the stirred dispersion of 0.27 g (1.25 mmol) of PCC in 4 ml of anhydrous CH_2Cl_2 at 0°C was added in one portion a solution of 0.12 g (0.71 mmol) of compound **I** in 2 ml of CH_2Cl_2. The reaction mixture was stirred for 2 h at 0°C, then at room temperature. It was filtered through a thin bed of silica gel, the solbent was washed with CH_2Cl_2 (5 × 3 ml), the combined extracts were dried with $MgSO_4$ and evaporated. The residue was subjected to chromatography on a column packed with SiO_2 (ethyl acetate–petroleum ether, 10 : 3) to obtain 0.04 g (55%) of oily mixture of enantiomers of **(5*R*,*S*)-5-acetyl-2-methylcyclohex-2-en-1-one (II),** $[\alpha]_D^{20}$ –15.0±5.0° (*C* 0.06, $CHCl_3$), $[\alpha]_D^{20}$ –2.5° (*C* 0.09, MeOH). ^{1}H NMR spectrum, δ, ppm: 1.79 s (3H, CH_3), 2.19 s (3H, CH_3), 2.51–2.56 m (3H, CH_2), 2.69 d.d (1H, CH_2, *J* 4.1, 16.4 Hz), 3.11 m (1H, CH), 6.70 m (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 15.68 (CH_3), 27.46 (C^4), 27.83 (CH_3), 39.41 (C^6), 48.13 (C^5), 135.90 (C^2), 142.61 (C^3), 197.46 (C=O), 207.82 (C^1). Found, %: C 71.55; H 8.02. $C_9H_{16}O_2$. Calculated, %: C 71.03; H 7.95.

Oxidation of epoxide III with periodic acid. To a solution of 0.16 g (0.9 mmol) of epoxide **III** in 30 ml of anhydrous ethyl ether at 0°C under an argon atmosphere was added 0.33 g (1.44 mmol) of periodic acid, and the mixture was stirred for 1 h at. Then the temperature was raised to ambient, and the mixture was stirred till complete disappearance of the epoxide (TLC monitoring). Afterwards the reaction mixture was washed with saturated solution of $NaHCO_3$, the water layer was extracted with ether (3 × 10 ml). The combined organic solutions were dried with $MgSO_4$, evaporated, the residue was subjected to chromatography on a column packed with SiO_2 (ethyl acetate–petroleum ether, 10 : 3) to obtain 0.12 g (82%) of individual 5R-isomer of diketone **II**.

(5*R*)-5-Acetyl-2-methylcyclohex-2-en-1-one (–)-

(II). $[\alpha]_D^{20}$ –75.1° (*C* 1.24, $CHCl_3$), $[\alpha]_D^{20}$ –53° (*C* 0.26, MeOH). Spectral characteristics coincide with those described above for the product obtained by the oxidation with PCC.

(5*R*)-2-Methyl-5-(2-methyloxiran-2-yl)cyclohex-2-en-1-one (III). To a dispersion of 0.44 g (2.55 mmol) of m-CPBA in 20 ml of anhydrous CH_2Cl_2 was added dropwise a solution of 0.25 g (1.7 mmol)of R-carvone in 5 ml of CH_2Cl_2, and the reaction mixture was stirred at room temperature till complete consumption of the initial compound (TLC monitoring). The reaction mixture was diluted with the saturated solution of $NaHCO_3$, the reaction products were extracted into CH_2Cl_2 (3 × 20 ml), the combined organic solutions were washed with brine, dried with $MgSO_4$, evaporated, the residue was subjected to chromatography on a column packed with SiO_2 (eluent EtOAc–petroleum ether, 1 : 2). Yield 0.18 g (72%), isomers mixture in a ratio 6 : 5 (according to the intensity of different doublet signals of the epoxide proton in the ^1H NMR spectrum).

Main isomer. ^1H NMR spectrum, δ, ppm: 1.31 s (3H, CH_3), 1.76 s (3H, CH_3), 2.00–2.60 m (6H, CH_2, CH, OCH_2), 2.65 d (1H, OCH_2, *J* 4.6 Hz), 6.72 br.s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 15.50 (CH_3), 18.22 (CH_3), 27.55 (C^4), 39.74 (C^6), 40.57 (C^5), 52.27 ($C^{3'}$), 57.73 ($C^{2'}$), 135.38 (C^2), 144.11 (C^3), 198.73 (C^1).

Minor isomer. ^1H NMR spectrum, δ, ppm: 1.29 C (3H, CH_3), 1.76 s (3H, CH_3), 2.00–2.60 m (6H, CH_2, CH, OCH_2), 2.69 d (1H, OCH_2, *J* 4.6 Hz), 6.72 br.s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 15.50 (CH_3), 18.77 (CH_3), 27.75 (C^4), 40.14 (C^6), 41.13 (C^5), 52.73 ($C^{3'}$), 57.84 ($C^{2'}$), 134.34 (C^2), 143.87 (C^3), 198.73 (C^1). Found, %: C 72.88; H 8.59. $C_{10}H_{14}O_2$. Calculated, %: C 72.26; H 8.46.

Reduction of epoxide III. To a solution of 0.50 g (3.0 mmol) of epoxide **III** in 10 ml of anhydrous MeOH was added 1.24 g (5.0 mmol) of $CeCl_3 \cdot 7H_2O$, and the mixture was stirred till it turned homogenic. Then at –10°C 0.125 g (3.00 mmol) of $NaBH_4$ was added, the temperature of the mixture was raised to ambient, and the stirring was continued till the disappearance of the initial ketone (TLC monitoring). The reaction mixture was evaporated, 5 ml of water was added, the reaction product was extracted into EtOAc (3 × 20 ml), the combined organic solutions were washed with brine, dried with $MgSO_4$, evaporated, the residue was subjected to chromatography on a column packed with SiO_2 (eluent EtOAc–petroleum ether, 1 : 1) to obtain 0.44 g (overall yield 80%) of a mixture of epimers of epoxyalcohol **V** and bicycle **I** in a ratio ~1 : 2 (according to the intensity of olefin protons in the ^1H NMR spectrum of the mixture). The mixture was chromatographed on SiO_2 to separate in two pairs of mixtures: **Va**, **Vb** + **Ia**, 1 : 1, and **Ib** + unidentified compounds, 3 : 1. The products were characterized by NMR spectra.

(1*S*,5*R*,7*R*)-(4,7-Dimethyl-6-oxabicyclo[3.2.1]-oct-3-en-7-yl)methanol (Ia). ^1H NMR spectrum, δ, ppm: 1.20 s (3H, CH_3), 1.69 d (3H, CH_3, *J* 1.7 Hz), 1.85 d (1H, *J* 10.5 Hz) and 2.17–2.23 m (5H, CH, CH_2), 3.56 d (1H, *J* 10.5 Hz) and 3.69 d (1H, OCH_2, *J* 10.8 Hz), 4.04 d (1H, C^5H, *J* 4.2 Hz), 5.24 br.s (1H, C^3H). ^{13}C NMR spectrum, δ, ppm: 19.78 (CH_3), 21.38 (CH_3), 29.46 (C^2), 34.88 (C^8), 40.57 (C^1), 69.97 (OCH_2), 76.62 (C^5), 84.76 (C^7), 121.04 (C^3), 139.32 (C^4).

(1*R*,5*R*,2'*RS*)-2-Methyl-5-(2-methyloxiran-2-yl) cyclohex-2-en-1-ol (Va, Vb). Mixture of diastereomers, 6 : 5. ^1H NMR spectrum, δ, ppm: 1.23 (1.24) s (3H, CH_3), 1.74 (1.76) s (3H, CH_3), 1.80–2.40 (6H, CH, CH_2, OH), 2.48–2.70 m (2H, OCH_2), 4.17 m (1H, C^1H), 5.50 br.s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 17.93 (18.56) (CH_3), 18.75 (18.86) (CH_3), 27.61 (27.74) (C^4), 35.13 (35.20) (C^6), 39.19 (39.83) (C^5), 53.20 (53.61) ($C^{3'}$), 58.73 (58.82) ($C^{2'}$), 70.16 (70.33) (C^1), 122.78 (123.02) (C^3), 136.70 (136.81) (C^2).

(1*S*,5*R*,7*S*)-(4,7-Dimethyl-6-oxabicyclo[3.2.1]-oct-3-en-7-yl)methanol (Ib). ^1H NMR spectrum, δ, ppm: 1.30 s (3H, CH_3), 1.71 d (3H, CH_3, *J* 1.8 Hz), 1.87 d (1H, *J* 10.0 Hz) and 2.00–2.23 m (6H, CH, CH_2, OH), 3.34 d (1H, OCH_2, *J* 10.8 Hz), 3.40 d (1H, OCH_2, *J* 10.8 Hz), 3.99 d (1H, C^5H, *J* 4.1 Hz), 5.24 br.s (1H, C^3H). ^{13}C NMR spectrum, δ, ppm: 21.43 (CH_3), 25.14 (CH_3), 30.13 (C^2), 34.53 (C^8), 38.40 (C^1), 67.64 (OCH_2), 76.96 (C^5), 84.76 (C^7), 120.04 (C^3), 139.65 (C^4).

(5*R*)-2-Methyl-5-(1-oxo-2-propyl)cyclohex-2-en-1-one (IV). To a solution of 0.13 g (0.78 mmol) of epoxide **III** in 10 ml of anhydrous CH_2Cl_2 was added dropwise 1 ml of $BF_3 \cdot Et_2O$, the reaction mixture was stirred at room temperature till complete consumption of the initial compound (TLC monitoring). To the reaction mixture 5 ml of saturated solution of NH_4Cl was added, the organic layer was separated, the water layer was extracted with CH_2Cl_2 (3 × 3 ml). The combined organic solutions were washed with brine, dried with $MgSO_4$, and evaporated. The residue was purified by column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 2). Yield 0.114 g(88%), mixture of diastereomers. Colorless oily substance, $[\alpha]_D^{20}$ –39.7° (*C* 4.28, $CHCl_3$). IR spectrum, cm^{-1}: 2974, 2922, 2885, 2717, 1724, 1674, 1452, 1433, 1367, 1147, 1107, 1074, 904, 754. ^1H NMR spectrum, δ, ppm: 0.99 t (1.02) (3H, CH_3, *J* 2.2 Hz), 1.69 s (3H, CH_3), 2.09–2.45 m (6H, CH, CH_2), 6.66 br.s (1H, =CH), 9.58 (9.60) d (1H, CHO, *J* 1.8 Hz). ^{13}C NMR spectrum, δ, ppm: 10.20 (9.94) (CH_3), 15.49 (CH_3), 30.22 (28.40) (C^4), 35.39 (C^5), 40.62 (41.70) (C^6), 49.92 ($C^{2'}$), 135.50 (C^2), 144.08 (C^3), 198.56 (C^1), 203.32 (CHO). Found, %: C 71.49; H 8.57. $C_{10}H_{14}O_2$. Calculated, %: C 72.26; H 8.49.

***tert*-Butyl{[(1*S*,5*R*,7*RS*)-4,7-dimethyl-6-oxabicyclo[3.2.1]oct-3-en-7-yl]methoxy}dimethylsilane (VI).** To a solution of 0.12 g (0.72 mmol) of the mixture of epoxyalcohol **V** and bicycle **I** in 10 ml of anhydrous CH_2Cl_2 was added 0.03 g (0.44 mmol) of imidazole, 0.11 g (0.72 mmol) of TBSCl, and a catalytic amount of DMAP. The reaction mixture was stirred till complete consumption of the initial compound (TLC monitoring), then it was diluted with CH_2Cl_2, washed with brine, dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 1). Yield 0.15 g (75%). Epimers mixture. Main isomer. ^1H NMR spectrum, δ, ppm: 0.01 s (6H, $SiMe_2$), 0.85 s (9H, $SiCMe_3$), 1.20 s (3H, CH_3), 1.68 d (3H, CH_3, *J* 1.8 Hz), 1.80 m (1H) and 2.10–2.40 m (4H, CH, CH_2), 3.30 d.d (2H, OCH_2, *J* 4.6 and 9.8 Hz), 3.93 d (1H, C^5H, *J* 4.6 Hz), 5.20 br.s (1H, C^3H). ^{13}C NMR spectrum, δ, ppm: –0.97 ($SiCH_3$), 18.12 ($\underline{C}Me_3$), 21.44 (CH_3), 25.51 (CH_3), 25.81 [$C(\underline{CH_3})_3$], 29.36 (C^8), 34.06 (C^2), 37.24 (C^1), 67.51 (OCH_2), 76.24 (C^5), 84.87 (C^7), 120.95 (C^3), 139.58 (C^4).

Minor isomer. ^1H NMR spectrum, δ, ppm: 0.01 s (6H, $SiMe_2$), 0.85 s (9H, $SiCMe_3$), 1.25 s (3H, CH_3), 1.70 d (3H, CH_3, *J* 1.8 Hz), 1.80 m (1H) and 2.10–2.40 m (4H, CH, CH_2), 3.55 d.d (2H, OCH_2, *J* 4.6 and 9.3 Hz), 4.02 d (1H, C^5H, *J* 4.4 Hz), 5.20 br.s (1H, C^3H). ^{13}C NMR spectrum, δ, ppm: –0.97 ($SiCH_3$), 18.26 ($\underline{C}Me_3$), 21.50 (CH_3), 25.63 (CH_3), 25.91 [$C(\underline{CH_3})_3$], 30.34 (C^8), 34.18 (C^2), 40.02 (C^1), 69.56 (OCH_2), 76.87 (C^5), 85.01 (C^7), 120.90 (C^3), 139.67 (C^4). Found, %: C 68.77; H 10.55; Si 10.22. $C_{16}H_{30}O_2Si$. Calculated, %: C 68.03; H 10.70; Si 9.94.

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