Organic Chemistry

Synthesis and ozonization of (+)-4α-(1-trimethylsilyloxyethen-1-yl)-2-carene

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(+)-4α-(1-Trimethylsilyloxyethen-1-yl)-2-carene was synthesized, and the products of its ozonization were identified.

Key words: (+)-4α-(1-trimethylsilyloxyethen-1-yl)-2-carene, (+)-4α-acetyl-2-carene, synthesis, ozonization.

Since (+)-4α-acetyl-2-carene (**1**) is a readily accessible compound[1] containing a double C=C bond at C(2) and a 2,2-dimethyl-1,3-disubstituted cyclopropane moiety, it can be used as a convenient and valuable starting compound for synthesizing optically active low-molecular bioregulators that contain *gem*-cyclopropane fragments.

In the present work, the silylation of compound **1** and ozonization of the product of its silylation, (+)-4α-(1-trimethylsilyloxyethen-1-yl)-2-carene (**2**), were studied. Silylation of **1** was carried out under standard conditions of kinetic[2] and thermodynamic[3] control. In the first case, silylenol ether **2** was formed in almost quantitative yield when the reaction with Me_3SiCl was carried out in the presence of LDA and THF.

The structure of compound **2** was confirmed by spectral data. The bands typical of the silyloxy group, trisubstituted double C=C bond, and silyloxyvinyl group were observed in its IR spectrum. The ^1H NMR spectrum of compound **2** contained a multiplet signal of protons of Me groups linked to the silicon atom at δ 0.01—0.11, singlet three-proton signals of the *gem*-dimethyl group at δ 0.75 and 0.93, and the Me group linked to the double bond at δ 1.70. The weak-field region contained a doublet two-proton signal of the vinyl $>C=CH_2$ group (δ 3.73—3.82) and a multiplet signal of the vinyl proton linked to the trisubstituted double bond at δ 5.27. The weak-field region of the ^{13}C NMR spectrum contained signals of four sp^2-hybridized carbon atoms, a doublet signal of the C(6) atom at δ 121.60, singlet signals of the C(7) and C(11) atoms at δ 136.29 and 159.80, respectively, and the triplet signal of the C(12) atom at δ 89.3. These data suggest that silylation affords compound **2**, which is a kinetically controlled reaction product.

Refluxing ketone **1** in a mixture of Et_3N, Me_3SiCl, and DMF, *i.e.*, under conditions of thermodynamic

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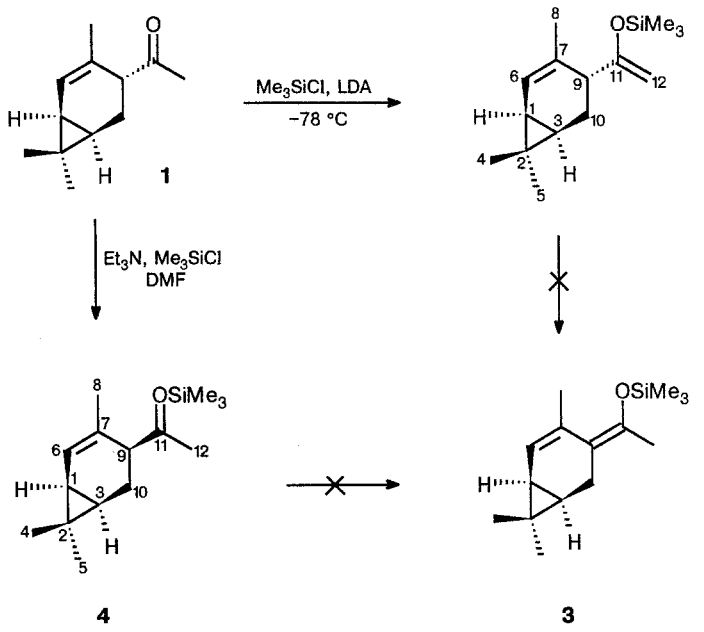
Scheme 1



control, resulted in epimer **4** of compound **2** rather than in the expected conjugated silylenol ether **3** (Scheme 1). The structure of ether **4** was confirmed by ^{1}H NMR spectroscopic data. Multiplet signals of nine protons of the trimethylsiloxy group at δ 0.14—0.2 and that of one vinyl proton at δ 5.45, singlet signals of the *gem*-dimethyl group (0.98 and 1.04 ppm) and that of the methyl group linked to the double bond at δ 1.70 are present in its ^{1}H NMR spectrum. The weak-field region (δ 0.4—4.06) contained a two-proton signal of the terminal C=C bond. The ^{13}C NMR spectrum of product **4** contained a triplet signal of the C(12) atom at 89.46 ppm, a doublet signal of the C(9) atom at δ 52.84, and singlet signals of the C(7) and C(11) atoms (δ 133.15 and 159.93, respectively). The above data combined with the IR and mass-spectroscopic data confirmed that the compound under study has structure **4**. In addition, absorption typical of the conjugated diene system was absent in the UV spectrum; this is also consistent with structure **4**. A molecular ion peak, *m/z* 250$^+$, and peaks of ions, *m/z* 115 [CH_2=C—$OSiMe_3$] and 73 [$SiMe_3$] (100 %), were observed in the mass spectrum.

Attempts to isomerize silylenol ether **2** into its dienic isomer **3** under standard conditions,[3,4] which are normally used for isomerizing kinetically controlled silylation products into thermodynamically controlled ones, *e.g.*, by prolonged boiling (48 h) with *p*-TsOH in CCl_4, failed.

The behavior of silylenol ether **2** during ozonization depends substantially on reaction conditions. When ozonization was carried out in CH_2Cl_2 in the presence of pyridine, a complex mixture of compounds was formed. We managed to perform chromatographic isolation on a SiO_2 column and characterize three of them.

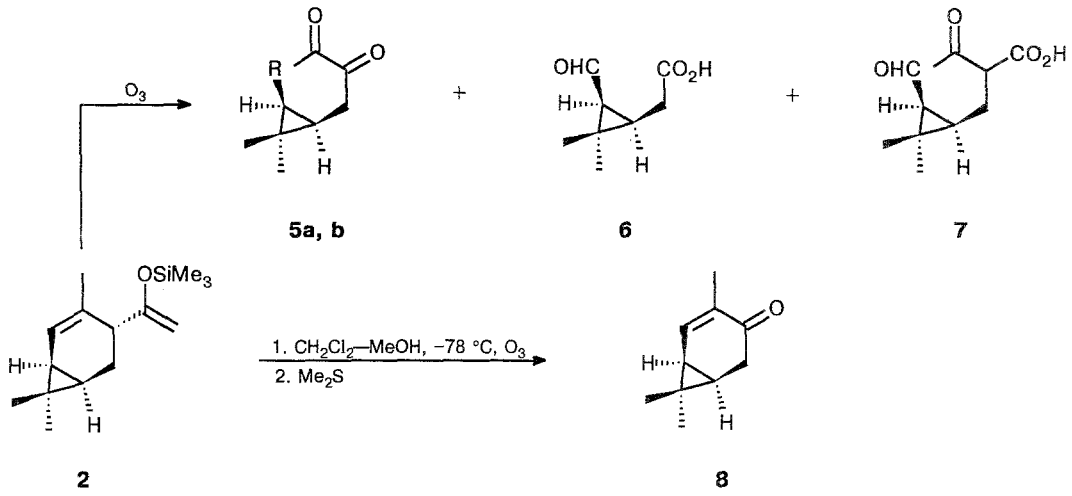
The least polar product was (+)(1*S*,3*R*)-1-formyl-2,2-dimethyl-3-(2,3-dioxobutyl)cyclopropane (**5a**) (~10 %). Maxima typical of the α-diketone and aldehyde groups were present in the IR spectrum of **5a**, and its ^{1}H NMR spectrum contained singlet signals of *gem*-dimethyl and methylketone groups and a doublet signal of the proton in the aldehyde group at δ 9.60. The structure of **5a** was also confirmed by the fact that acetalization of compound **5a** with MeOH in the presence of NH_4Cl afforded α-diketoacetal (**5b**) described previously[6] (Scheme 2).

The medium-polarity product was found to be (+)(1*S*,3*R*)-1-formyl-2,2-dimethyl-3-(carboxymethyl)-cyclopropane (**6**) (~15 %). The IR spectrum of this compound contained bands typical of the carboxyl and aldehyde groups, and its ^{1}H NMR spectrum contained signals of the *gem*-dimethyl group, a proton at C(1) in the cyclopropane ring (a doublet at δ 2.81), and signals of aldehyde protons (a doublet at δ 9.83) and carboxyl group protons (δ 10.65). A doublet signal of carbon atoms of the aldehyde group (201.64 ppm) and of a carbon atom of the carboxyl group (177.8 ppm) appeared in the weak-field region of its ^{13}C NMR spectrum.

The most polar product appeared to be (+)(1*S*,3*R*)-1-formyl-2,2-dimethyl-3-(2-carboxy-3-oxobutyl)cyclopropane (**7**) (~5 %). Its IR spectrum contained bands of aldehyde, methylketone, and carboxyl groups. The ^{1}H NMR spectrum of compound **7** contained a triplet signal of a proton at the tertiary carbon atom, which is linked to the carboxyl and methylketone groups, at δ 3.25, a one-proton doublet of aldehyde, and a singlet signal of the carboxyl group at δ 9.86 and 10.51, respectively.

Ozonization of ether **2** occurred in different ways and more unambiguously when the reaction was carried out in a CH_2Cl_2—MeOH mixture (1 : 1) followed by decomposition of peroxide products with Me_2S. The nature of

Scheme 2



5a: R = CHO

5b: R = (MeO)CH

the products formed depended significantly on the quantity of ozone passed through the solution. Caren-2-one (**8**) was the product when 1 mol of ozone was used. Ketone **8** was identified on the basis of spectral data. Its UV spectrum with maxima at 262 and 327 nm and IR spectrum (maxima at 850, 1600, and 1690 cm^{-1}) indicated the existence of a conjugated keto group. The ^1H NMR spectrum contained three-proton signals of a *gem*-dimethyl group at δ 0.80 and 1.12 and that of a methyl group at the double bond, a two-proton multiplet of the methyl group at the α-position to the keto group (δ 2.51), and a one-proton multiplet of the vinyl proton at δ 6.67. The weak-field region of the ^{13}C NMR spectrum of compound **8** contained signals of three sp^2-hybridized carbon atoms: a doublet at δ 144.98 (C(2)) and singlets at δ 145.77 (C(3)) and 196.16 (C=O). These data combined with elemental analysis data indicate that the compound under study has structure **8**. A molecular ion peak, *m/z* 150, and ion peaks, *m/z* 135 $[M—Me]^+$, 107 $[M—Pr]^+$, and 43 $[Pr]^+$, were observed in the mass spectrum of this compound.

It is noteworthy that compound **8** has been described previously[6,7,8] but its spectral parameters have not been reported.

If ozonization of enol ether **2** was carried out in the same mixture of solvents but with two equivalents of ozone, the main product of the reaction appeared to be α-diketoaldehyde **5a** (70 %), and aldehydoacids **6** (10 %) and **7** (7 %) were the minor products.

Hence, the type of the products formed and their quantitative ratio depend substantially on ozonization conditions. Taking into account the structure of the starting enol ether **2**, the formation of both caren-2-one (**8**) and α-diketoaldehyde **5a** was unexpected. This allows us to conclude that ozonization may involve isomerization to form conjugated dienolsilyl ether **3**.

Experimental

Specific rotation was determined on a Perkin—Elmer 141 polarimeter in $CHCl_3$. IR spectra were obtained on Specord 74-1 and UR-20 instruments. UV spectra were recorded on a Shimadsu UV-365 spectrometer in pentane. ^1H NMR spectra were obtained on Tesla BS-487 and BS-567 spectrometers, and ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.5 MHz) instrument in $CDCl_3$ using $SiMe_4$ as the internal standard. Chemical shifts are given on the δ scale. Mass spectra were recorded on an MX-1320 spectrometer equipped with a system for direct introduction of substances into the ion source; the ionizing voltage was 70 eV.

Solutions of substances in organic solvents were washed with water until neutral reaction. Acidic solutions were washed with water, a 5 % solution of potassium hydroxide, and water, dried with anhydrous $MgSO_4$ or Na_2SO_4, and filtered, and the solvent was distilled off *in vacuo* produced by a water-jet pump.

(+)-4α-Acetyl-2-carene (1) was obtained according to a procedure described previously,[1] n_D^{20} 1.4869, $[\alpha]_D^{20}$ +365.5° (in a pure state) (*cf.* Ref. 1: n_D^{20} 1.4848, $[\alpha]_D^{20}$ +402°).

(+)-4α-(1-Trimethylsilyloxyethen-1-yl)-2-carene (2). Diisopropylamine (5 g, 0.049 mol) and a solution of *n*-butyllithium (2.45 *M*) in hexane (20.6 mL) were added to dry THF (100 mL) at −18 °C. The mixture was stirred for 10 min, then the temperature was lowered to −78 °C, and a solution of ketone **1** (8.02 g, 0.045 mol) in THF (15 mL) was added dropwise. The mixture was stirred for 10 min, then Me_3SiCl (12 mL, 0.094 mol) was added, and the mixture was allowed to reach room temperature. The mixture was stirred for 2 h and poured into dry pentane (150 mL). The solution was filtered, and the solvent was distilled off to give 10.9 g (97 %) of ether **2** as a yellow liquid, b.p. 112—118 °C (2 Torr), n_D^{20} 1.4750, $[\alpha]_D^{20}$ +61.91° (*c* 3.0, pentane). IR (CCl_4), ν/cm^{-1}: 840 (C=CH), 1020, 1265 (C—O—$SiMe_3$), 1370, 1375 (C, Me_2), 1640 (C=CH), 1650 (C=CH_2). ^1H NMR ($CDCl_3$), δ:

0.01—0.11 (m, 9 H, $OSiMe_3$); 0.75 (s), 0.93 (s, 6 H, CMe_2); 1.0—1.25 (m, 1 H, HC(3)); 1.60 (s, 3 H, MeC=C); 1.61—2.4 (m, 4 H, HC(1), CH_2=C—CH—C=); 3.73—3.82 (m, 2 H, C=CH_2); 5.27 (m, 1 H, HC=C). ^{13}C NMR ($CDCl_3$), δ: 159.80 (s, C(11)); 136.29 (s, C(7)); 121.60 (d, C(6)); 89.3 (t, C(12)); 52.68 (d, C(9)); 27.41 (t, C(8)); 27.61 (t, C(10)); 23.62 (q, C(5)); 23.30 (s, C(2)); 22.45 (d, C(1)); 17.88 (q, C(4)); 14.88 (d, C(3)). UV, λ_{max}/nm (ε): 263 (2933).

(+)-4β-(1-Trimethylsilyloxyethen-1-yl)-2-carene (4). Ketone **1** (3.4 g, 0.02 mol) was added to a solution of Me_3SiCl (2.6 g, 0.02 mol) and Et_3N (4.8 mL, 0.048 mol) in DMF (8 mL). The mixture was refluxed with stirring for 56 h, then dry ether (200 mL) was added, and the solution was filtered. The solvent was distilled off, and the residue (5.1 g) was distilled under a reduced pressure to give 3.34 g (70 %) of a pale yellow liquid, b.p. 110—113 °C (2 Torr), n_D^{20} 1.4690, $[\alpha]_D^{20}$ +48.7° (*c* 3.0, pentane). IR (CCl_4), ν/cm^{-1}: 843 (C=CH); 1020, 1265 (C—O—$SiMe_3$, 1375, 1380 (CMe_2); 1655 (C=CH_2); 1670 (C=CH). ^1H NMR ($CDCl_3$), δ: 0.14—0.2 (m, 9 H, $OSiMe_3$); 0.98 (s), 1.04 (s, 6 H, CMe_2); 1.10—1.32 (m, 1 H, HC(3)); 1.70 (s, 3 H, CH_3C=C); 1.65—2.52 (m, 4 H, HC(1), $-CH_2-$, =C—CH—C=); 4.00—4.06 (m, 2 H, C=CH_2); 5.45 (m, 1 H, C=CH). ^{13}C NMR ($CDCl_3$), δ: 159.93 (s, C(11)); 133.15 (s, C(7)); 121.79 (d, C(6)); 89.46 (t, C(12)); 52.84 (d, C(9)); 27.61 (q, C(8)); 23.83 (s, C(2)); 27.61 (t, C(10)); 23.23 (q, C(5)); 22.62 (d, C(1)); 18.03 (C(4)); 15.04 (d, C(3)). MS, *m/z*: 250, 135, 115 [CH_2=C—$OSiMe_3$], 73 [$SiMe_3$] (max).

(+)(1*S*,3*R*)-1-Formyl-2,2-dimethyl-3-(2,3-dioxobutyl)cyclopropane (5a). A. An ozone—oxygen mixture was passed through a stirred solution of ether **2** cooled to −78 °C (5 g, 0.019 mol) in a mixture of CH_2Cl_2 (25 mL) and pyridine (1.3 mL) until ozone began to get through the solution. Then N_2 was bubbled through the solution, which was then kept until it reached room temperature. Ether (150 mL) was added to the mixture, and the solution was acidified with 5 % H_2SO_4. The organic layer was separated and treated in the usual way. The residue (5.1 g) was chromatographed on SiO_2 L40/100. Elution with a hexane—ethyl acetate mixture (3 : 1) afforded 0.36 g (10 %) of unstable liquid diketoaldehyde **5a**, n_D^{20} 1.4810, $[\alpha]_D^{20}$ +17.6° (*c* 0.91). Found (%): C, 65.86; H, 7.71. $C_{10}H_{14}O_3$. Calculated (%): C, 65.92; H, 7.73. IR (CCl_4), ν/cm^{-1}: 1380, 1385(CMe_2);1690, 1715, 2750 (C=O, CHO). ^1H NMR (CCl_4), δ: 1.18 (s), 1.27 (s, 6 H, CMe_2); 0.8—1.9 (m, 2 H, HC(1), HC(3)); 2.07 (s, 3 H, MeCO); 2.0—2.4 (m, 2 H, CH_2); 9.6 (d, 1 H, CHO, J = 3 Hz).

B. Compound **2** (5 g, 0.019 mol) was ozonized in a CH_2Cl_2—MeOH (1 : 1) mixture (60 mL) at −78 °C until two equivalents of ozone were absorbed. Argon was bubbled through the solution, then Me_2S (8.5 mL) was added, and the mixture was stirred for 2 h and left until it reached room temperature. The solution was concentrated to half volume, diluted with ether, and treated in the usual way. Chromatography on SiO_2 afforded 2.54 g (70 %) of diketoaldehyde **5a**, which was identical to that described above.

(+)(1*S*,3*R*)-1-Formyl-2,2-dimethyl-3-(carboxymethyl)cyclopropane (6). A. Ozonization of siloxyether **2** (5 g, 0.019 mol) in a CH_2Cl_2—pyridine mixture followed by chromatography of the reaction products (see the synthesis of compound **5a**) gave 0.46 g (15 %) of oily yellow compound **6**. Found (%): C, 61.50; H, 7.69. $C_8H_{12}O_3$. Calculated (%): C, 61.52; H, 7.74. IR (CCl_4), ν/cm^{-1}: 1375, 1382 (CMe_2); 1700, 2750, 2400—3000 (CHO, CO_2). ^1H NMR ($CDCl_3$), δ: 123 (s, 6 H, CMe_2); 1.05—1.65 (m, 2 H, HC(1), HC(3)); 2.81 (d, 2 H, CH_2, J = 6.6 Hz); 9.83 (d, 1 H, CHO, J = 3 Hz), 10.65 (s, 1 H, CO_2H). ^{13}C NMR ($CDCl_3$), δ: 201.64 (d, CHO); 177.8 (s, CO_2); 30.89 (d, HC(1)), 28.65 (t, CH_2); 28.07 (d, HC(3)); 26.5 (s, $\underline{C}Me_2$); 28.53 (q), 14.17 (q, CMe_2).

B. Ozonization of ether **2** (5 g, 0.019 mol) in a CH_2Cl_2—MeOH mixture followed by chromatography of the reaction products gave 10 % of compound **6**, which was identical to that described in procedure **A**.

(+)(1*S*,3*R*)-1-Formyl-2,2-dimethyl-3-(2-carboxy-3-oxobutyl)cyclopropane (7). Chromatography of the products of ozonization of ether **2** (5 g, 0.019 mol) (see the synthesis of compound **5a**) according to procedures **A** and **B** gave 0.21 g (5 %) and 0.29 g (7 %) of oily compound **7**, respectively. Found (%): C, 62.25; H, 7.59. $C_{11}H_{16}O_4$. Calculated (%): C, 62.26; H, 7.59. IR (CCl_4), ν/cm^{-1}: 1380, 1385 (CMe_2); 1705 (C=O); 2750 (CHO); 2400—2900 (CO_2H). ^1H NMR (CCl_4), δ: 0.9—2.28 (m, 4 H, HC(1), HC(3), CH_2); 1.15 (s), 1.26 (s, 6 H, CMe_2); 2.53 (s, 3 H, COMe); 3.25 (t, 1 H, $CHCO_2H$, J = 4.5 Hz); 9.86 (d, 1 H, CHO, J = 3.1 Hz); 10.51 (s, 1 H, CO_2H).

Caren-2-one (8). Ozonization of ether **2** (5 g, 0.019 mol) in a CH_2Cl_2—MeOH (1 : 1) mixture with one equivalent of ozone followed by decomposition of peroxide products with Me_2S (5 mL) (similarly to the synthesis of compound **5a**, procedure **B**) and the usual treatment afforded 3.4 g of a residue. The residue was purified on a SiO_2 (120 g) L40/100 column and eluted with a hexane—ether (10 : 1) mixture to give 2.09 g (70 %) of liquid ketone **8**, n_D^{20} 1.4700 and $[\alpha]_D^{20}$ +239.3° (*c* 0.6). Found (%): C, 79.89; H, 9.35. $C_{10}H_{14}O$. Calculated (%): C, 79.96; H, 9.38. IR (CCl_4), ν/cm^{-1}: 825 (C=C); 1375, 1390 (CMe_2); 1690 (C=C); 1705 (C=O). ^1H NMR ($CDCl_3$), δ: 0.80 (s), 1.12 (s, 6 H, CMe_2); 1.46—1.61 (m, 1 H, HC(3)); 1.78—1.86 (m, 1 H, HC(1)); 2.27 (s, 3 H, Me—C=C); 2.42—2.60 (m, 2 H, CH_2); 6.66—6.68 (m, 1 H, HC=C). ^{13}C NMR ($CDCl_3$), δ: 38.58 (d, HC(1)); 144.98 (d, HC=C); 145.77 (s, C=CH); 196.16 (s, C=O); 30.55 (t, CH_2); 31.14 (d, HC(3)); 23.70 (s, CMe_2); 13.18 (q), 26.57 (q, CMe_2); 26.37 (q, MeC=). MS, *m/z*: 150, 135 (M−Me), 119, 107 (M—Pr), 93, 91, 79, 77, 65, 43 (Pr). UV, λ_{max}/nm (ε): 262 (6825), 327 (140) (*cf.* Ref. 8: n_D^{27} 1.5270, $[\alpha]_D$ +5.24°, in pure state).

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