Some features of $RuCl_3$-catalyzed periodate oxidation of 3-*N*-substituted 5-allenyl-2,5-dichloro-4,4-dimethoxycyclopent-2-en-1-ones

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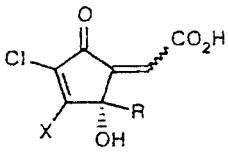
3-*N*-Substituted 5-(1*Z*-carboxymethylene)-2-chloro-4,4-dimethoxycyclopent-2-en-1-ones have been prepared from the corresponding 3-*N*-substituted 5-allenyl-2,5-dichloro-4,4-dimethoxycyclopent-2-en-1-ones using selective oxidative cleavage of their allene bond by the $RuCl_3$—$NaIO_4$ system.

Key words: allenylcyclopentenone, periodate oxidation; *Z*-carboxymethylenecyclopentenones; intramolecular hydrogen bond.

One of the key steps of our research into the synthesis of structures that could be pharmacologically promising analogs of sea prostanoids of the general formula **1** (X = NR^1R^2, OR, SR, Hal, H, *etc.*; R — alkyl, alkenyl, aryl, *etc.*) from hexachlorocyclopentadiene[1,2] is the construction of the *exo*-carboxymethylene moiety of these compounds. For this purpose, in this study we have synthesized 3-*N*-substituted 5-allenyldichlorocyclopentenones **3a—d** from 5-allenyl-2,3,5-trichloro-4,4-dimethoxycyclopentenone (**2**)[3] and studied oxidative cleavage of compounds **3a—d** under the action of a $RuCl_3 \cdot 3H_2O$—$NaIO_4/CCl_4$—MeCN—H_2O system.[4]



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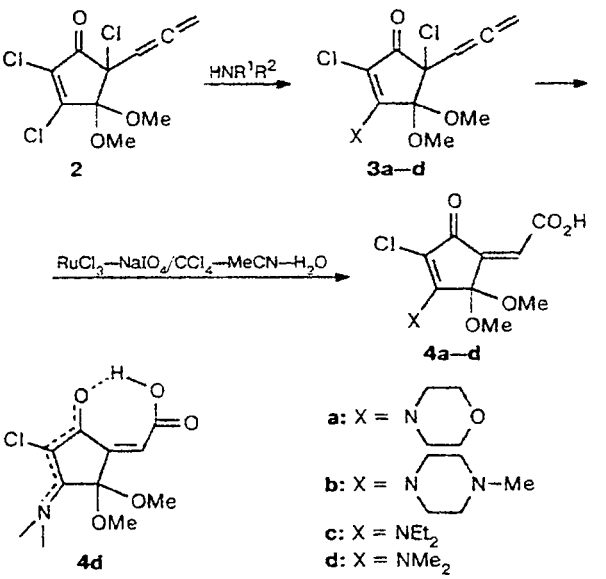
Although this oxidative system is not highly chemoselective[5] (RuO_4, which is responsible for the catalyzed oxidative cycle, interacts with alkenes, alkynes, aromatic compounds, alcohols, ethers, *etc.* in the presence of cooxidants), we demonstrated earlier that the abnormal reaction of the formation of iodohydrin, 2,5-dichloro-5-(2-hydroxy-3-iodopropyl)-4,4-dimethoxy-3-morpholinocyclopent-2-en-1-one, occurs smoothly in the oxidation of 5-allyl-2,5-dichloro-4,4-dimethoxy-3-morpholinocyclopent-2-en-1-one.[6] Therefore, the dimethylacetal group, the ring double bond, and other potentially reactive N- and Cl-containing centers in molecules **3a—d** should also be tolerant to the action of this oxidizing agent. At the same time, the allene π-system of compounds **3a—d**, which is more electrophilic and reactive than the allylic system in 5-allyl-2,5-dichloro-4,4-dimethoxy-3-morpholinocyclopent-2-en-1-one, obviously should more easily undergo attack by RuO_4, which is directed preferably at the terminal allene bond for steric reasons. These assumptions were confirmed experimentally. The $RuCl_3$-catalyzed periodate oxidation of cyclopentenones **3a—d** proceeded chemo-, regio-, and stereoselectively to give 5*Z*-carboxymethylenecyclopentenones **4a—d** in high yields (Scheme 1).

Scheme 1



The exclusively stereoselective formation of 5*Z*-isomeric acids **4a—d** engaged our attention: the corresponding 5*E*-isomers were not found. The *Z*-orientation of the exocyclic carboxymethylene moiety in molecules **4a—d** was unambiguously confirmed by X-ray diffraction analysis data for one of these compounds, dimethylamino derivative **4d**.[7] The X-ray diffraction analysis data

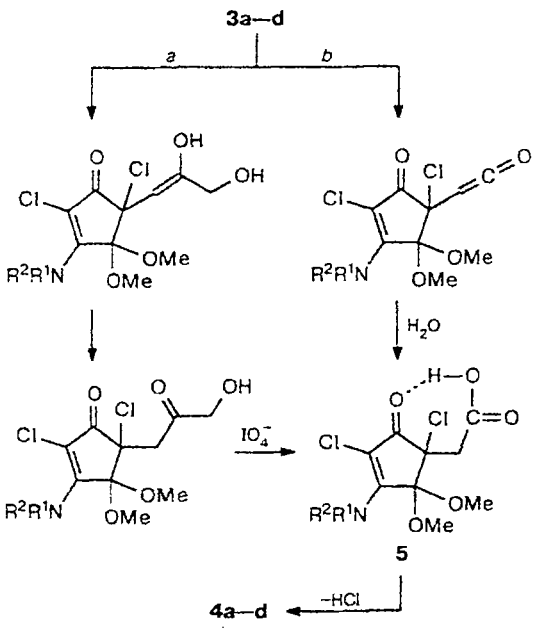
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 9, pp. 1646—1648, September, 1997.

1066-5285/97/4609-1569 $18.00 © 1997 Plenum Publishing Corporation

indicate that a strong intramolecular H-bond exists between the carboxy group proton and the oxygen of the C(1)=O moiety, and n- and π-electrons are delocalized throughout the system of conjugated bonds of compound **4d**. The chelate H-bond-stabilized 5*Z*-stereochemistry of the synthesized acids is also confirmed by the absence of COOH group absorption in the region of 3000—3600 cm^{-1} in the IR spectra, by the abnormally low-field chemical shifts of the acid proton in the ^1H NMR spectra (δ 15—16) that are independent of dilution, and by the diastereotropism of the protons of NMe_2 (**4d**) and α,α-CH_2 groups (**4a—c**).

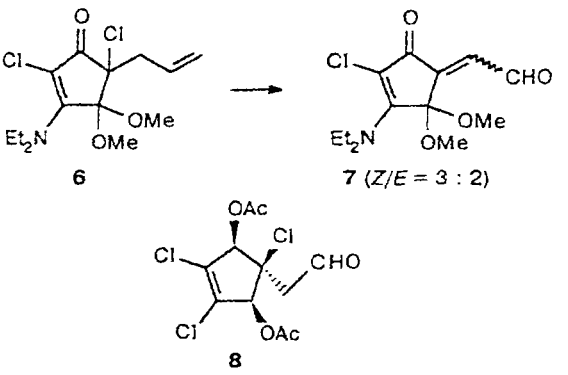
Undoubtedly the mechanistic aspects of the stereoselective formation of 5*Z*-acids **4a—d** are of interest. Taking into account the facts mentioned above, the possible pathways of oxidative degradation of the allene moiety in compounds **3a—d** by a $RuCl_3$—$NaIO_4$ system (Scheme 2, *a* and *b*) should include the formation of the intermediate β-chloroacid **5**, which at the moment of its generation is "drawn into" the chelate cycle by the electron-enriched CO group of the chlorovinyl enaminoketone moiety of the molecule. This ensures ease of the reaction and stereospecificity at the step of HCl elimination.

Scheme 2



The absence of stereoselectivity in the similar OsO_4 catalyzed periodate oxidation of compound **6** to form a mixture of enals **7**,[2] and isolation of intermediate β-chloroaldehyde **8** in the similar oxidation of the corresponding olefin[8] (Scheme 3) also confirm the proposed mechanism.

Scheme 3



Experimental

IR spectra were recorded on an UR-20 spectrophotometer (as thin layers or as Nujol mulls). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75.47 MHz, respectively) in $CDCl_3$ or in $(CD_3)_2CO$; $SiMe_4$ was used as the internal standard. Compounds **2**, **3a**, and **3d** were synthesized by earlier reported procedures.[9,10]

(±)-5-Allenyl-2,5-dichloro-4,4-dimethoxy-3-(*N*-methylpiperazino)cyclopent-4-en-1-one (3b). A solution of *N*-methylpiperazine (0.9 g, 9.8 mmol) in MeOH (10 mL) was added to a solution of trichloroallene **2** (1.3 g, 4.6 mmol) (see Ref. 9) in MeOH (30 mL). The reaction mixture was stirred at ~20 °C for 4 to 5 h until the starting compound completely disappeared (TLC). The methanol was evaporated, and water (20 mL) was added to the resulting residue. The products were extracted with CH_2Cl_2 (4×30 mL). The combined extracts were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated. Recrystallization of the residue from a pentane—ethyl acetate mixture (1 : 1) gave compound **3** (1.46 g, 92%), m.p. 78.0—79.5 °C. IR, ν/cm^{-1}: 735, 900, 940, 960, 1615, 1650, 1715, 2815. ^1H NMR ($CDCl_3$), δ: 2.04 (s, 3 H, CH_3N); 3.30, 3.48 (both s, 3 H each, OCH_3); 3.8—4.0 (m, 8 H, CH_2); 4.39 (dd, 2 H, CH_2, J = 2.6 and 6.6 Hz); 5.42 (t, 1 H, CH=, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 45.73 (CH_3N); 48.71 (CH_2N); 51.78, 53.47 (OCH_3); 55.32 (CH_2N); 72.62 (C(5)); 80.38 (=CH_2); 92.53 (=CH); 102.83 (C(4)); 105.27 (C(2)); 158.15 (C(3)); 185.37 (C(1)); 208.49 (=C=). Found (%): C, 50.80; H, 5.67; Cl, 20.80; N, 7.90. $C_{15}H_{20}Cl_2N_2O_3$. Calculated (%): C, 51.87; H, 5.76; Cl, 20.46; N, 8.07.

(±)-5-Allenyl-2,5-dichloro-3-diethylamino-4,4-dimethoxycyclopent-4-en-1-one (3c) was obtained analogously to compound **3b** from trichloroallene **2** (1 g, 3.54 mmol) and diethylamine (0.52 g, 7.07 mmol), m.p. 62.0—63.5 °C. IR, ν/cm^{-1}: 745, 910, 1595, 1700, 1960. ^1H NMR ($CDCl_3$), δ: 1.19 (t, 6 H, CH_3, J = 6.84 Hz); 3.26, 3.39 (both s, 3 H each, OCH_3); 3.72 (m, 4 H, CH_2); 4.95 (dd, 2 H, CH_2=, J = 6.37 and 3.3 Hz); 5.40 (t, 1 H, CH=, J = 6.36 Hz). ^{13}C NMR ($CDCl_3$), δ: 14.05 (CH_3); 51.14, 52.90 (OCH_3); 60.19 (CH_2N); 72.25 (C(5)); 79.85 (CH_2=); 92.67 (CH=); 101.16 (C(4)); 105.0 (C(2)); 157.94 (C(3)); 184.89 (C(1)); 208.09 (=C=). Found (%): C, 50.8; H, 5.8; Cl, 21.96; N, 4.2. $C_{14}H_{19}Cl_2NO_3$. Calculated (%): C, 52.5; H, 5.93; Cl, 22.19; N, 4.38.

5-(1*Z*-Carboxymethylene)-2-chloro-4,4-dimethoxy-3-morpholinocyclopent-2-en-1-one (4a). $RuCl_3 \cdot 3H_2O$ (*ca.* 2 g) was added to a stirred suspension of dichloroketone **3a** (see Ref. 10) (0.10 g, 0.3 mmol) and $NaIO_4$ (0.14 g, 0.65 mmol) in a CCl_4—AcCN—H_2O mixture (2 : 2 : 3, v/v). The reaction mixture was stirred for 4—5 h at ~20 °C. Then CH_2Cl_2 (10 mL) was added to the resulting mixture, the organic layer was separated, and the water layer was extracted with CH_2Cl_2 (4×30 mL). The combined organic extracts were dried over $MgSO_4$, filtered off, evaporated, and the residue was crystallized from diethyl ether. Compound **4a** (0.09 g, 95%) was obtained as a light yellow crystalline solid, m.p. 204—206 °C. IR, ν/cm^{-1}: 910, 930, 955, 990, 1560, 1715, 2745. ^1H NMR ($CDCl_3$), δ: 3.29 (s, 6 H, OCH_3); 3.83—3.88 (m, 4 H, CH_2N); 4.08, 4.31 (both m, 2 H each, OCH_2); 6.16 (s, 1 H, =CH). ^{13}C NMR ($CDCl_3$), δ: 49.17, 50.36 (CH_2N); 52.39 (OCH_3); 67.09, 67.34 (CH_2O); 103.93 (C(4)); 109.62 (C(2)); 124.72 (CH=); 137.99 (C(5)); 159.97 (C(3)); 164.82 (CO_2H); 182.24 (C(1)). Found (%): C, 49.00; H, 4.85; Cl, 11.23; N, 4.50. $C_{13}H_{16}ClNO_6$. Calculated (%): C, 49.21; H, 5.04; Cl, 11.04; N, 4.41.

5-(1*Z*-Carboxymethylene)-2-chloro-4,4-dimethoxy-3-(*N*-methylpiperazino)cyclopent-2-en-1-one (4b) was synthesized similarly to compound **4a** from ketone **3b** (1.46 g, 4.2 mmol) and $NaIO_4$ (3.90 g, 18 mmol), yield 1.30 g (93%), m.p. 119—121 °C (decomp.) (bright yellow crystals). IR, ν/cm^{-1}: 750, 920, 1000, 1605, 1665, 1725, 2750. ^1H NMR ($(CD_3)_2CO$), δ: 2.75 (s, 3 H, CH_3N); 3.43 (s, 6 H, OCH_3); 3.24—3.50 (m, 4 H, CH_2); 4.26—4.68 (m, 4 H, CH_2); 6.14 (s, 1 H, CH=). ^{13}C NMR ($(CD_3)_2CO$), δ: 42.98 (NCH_3); 45.65, 53.46 (CH_2N); 51.30, 51.82 (OCH_3); 103.61 (C(4)); 109.67 (C(2)); 124.31 (CH=); 137.51 (C(5)); 160.22 (C(2)); 164.00 (CO_2H); 182.34 (C(1)). Found (%): C, 49.75; H, 5.73; Cl, 10.41; N, 8.21. $C_{14}H_{19}ClN_2O_5$. Calculated (%): C, 50.83; H, 5.75; Cl, 10.74; N, 8.47.

5-(1*Z*-Carboxymethylene)-2-chloro-3-diethylamino-4,4-dimethoxycyclopent-2-en-1-one (4c) was synthesized similarly to compound **4a** from ketone **3c** (0.30 g, 0.94 mmol) and $NaIO_4$ (0.42 g, 1.96 mmol), yield 0.13 g (50%, in view of conversion), m.p. 132—134 °C. IR, ν/cm^{-1}: 725, 905, 920, 990, 1640, 1690, 1725, 2770, 3030, 3070. ^1H NMR ($CDCl_3$), δ: 1.34 (t, 3 H, CH_3, J = 7.01 Hz); 1.39 (t, 3 H, CH_3, J = 7.09 Hz); 3.29 (s, 6 H, OCH_3); 3.97 (q, 2 H, OCH_2, J = 7.05 Hz); 4.0 (q, 2 H, OCH_2, J = 7.08 Hz); 6.19 (s, 1 H, =CH). ^{13}C NMR ($CDCl_3$), δ: 13.7, 15.7 (CH_3); 45.3, 46.92 (CH_2N); 52.17 (OCH_3); 103.93 (C(4)); 109.63 (C(2)); 123.87 (=CH); 138.77 (C(5)); 160.78 (C(3)); 165.16 (CO_2H); 181.46 (C(1)). Found (%): C, 52.20; H, 5.90; Cl, 10.26; N, 4.35. $C_{13}H_{18}ClNO_5$. Calculated (%): C, 51.49; H, 5.94; Cl, 11.55; N, 4.62.

5-(1*Z*-Carboxymethylene)-2-chloro-4,4-dimethoxy-3-dimethylaminocyclopent-2-en-1-one (4d) was synthesized similarly to compound **4a** from ketone **3d** (0.20 g, 0.6 mmol) and $NaIO_4$ (0.28 g, 1.3 mmol), yield 0.17 g (90%), crystals, m.p. 144—145 °C. IR, ν/cm^{-1}: 725, 905, 920, 990, 1640, 1690, 1725, 2770, 3030, 3070. ^1H NMR ($CDCl_3$), δ: 3.30 (s, 6 H, OCH_3); 3.52, 3.70 (both s, 3 H each, Me_2N); 6.10 (s, 1 H, CH=). ^{13}C NMR ($CDCl_3$), δ: 42.29, 42.45 (Me_2N); 52.04 (OCH_3); 103.53 (C(4)); 110.09 (C(2)); 123.72 (CH=); 138.88 (C(5)); 161.96 (C(3)); 164.99 (CO_2H); 181.74 (C=O). Found (%): C, 46.95; H, 5.04; Cl, 12.01; N, 4.95. $C_{11}H_{14}ClNO_5$. Calculated (%): C, 47.91; H, 5.08; Cl, 12.89; N, 5.08.

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Received April 7, 1997;
in revised form May 12, 1997