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New Nitrogen- and Sulfur-Containing Derivatives of Chlorocyclopentenones

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Abstract—Reactions of 2,3,5-trichloro-4,4-ethylenedioxy- and 2,3,5-trichloro-5-(1,1-dimethylprop-2-en-1-yl)-4,4-dimethoxycyclopent-2-en-1-ones with amino acids gave products of Ad_NE substitution at the C^3 atom, the corresponding vinylogous amides. Sodium carbamodithioates generated *in situ* from amines, carbon disulfide, and sodium hydride in tetrahydrofuran reacted with di- and trichlorocyclopentenones in a similar way. Cyanosilylation of 2,3,5-trichloro-4,4-ethylenedioxycyclopent-2-en-1-one with trimethylsilyl cyanide smoothly occurred in toluene at 25°C in the presence of glycine as catalyst.

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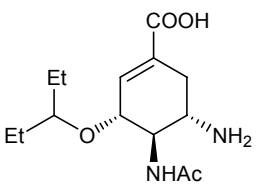
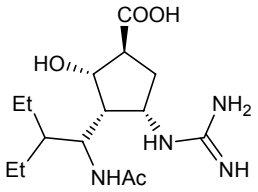
A promising line in the development of antiviral agents implies design and synthesis of inhibitors of neuraminidase which is an enzyme residing on the surface of virus species and responsible for decomposition of terminal sialic acids in glycoproteins and for promotion of separation of mature viruses from infected cells, etc. [1, 2]. Among neuraminidase inhibitors, the most potent is diaminocyclohexenecarboxylic acid derivative **I** which is known under the trade name *Tamiflu*. A number of novel procedures for the synthesis of compound **I** were proposed in the recent years [3–5]. Another promising representative of carbocyclic neuraminidase inhibitors is strongly functionalized cyclopentanecarboxylic acid **II** (BCX-1812); it is now under final step of clinical trial [6].

We set ourselves the task of synthesizing new antiviral agents of the cyclopentane series containing functionally important fragments like **I** and **II**. As key



I



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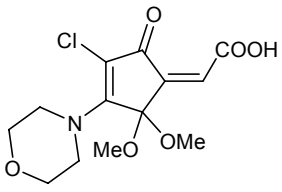
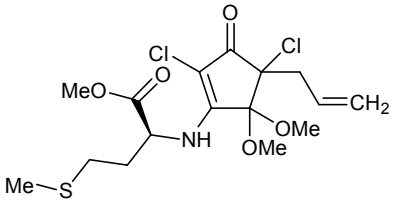
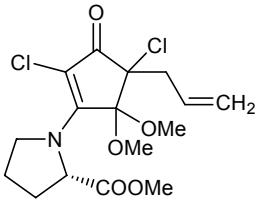


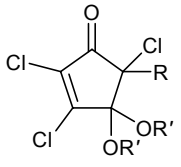
III



IV



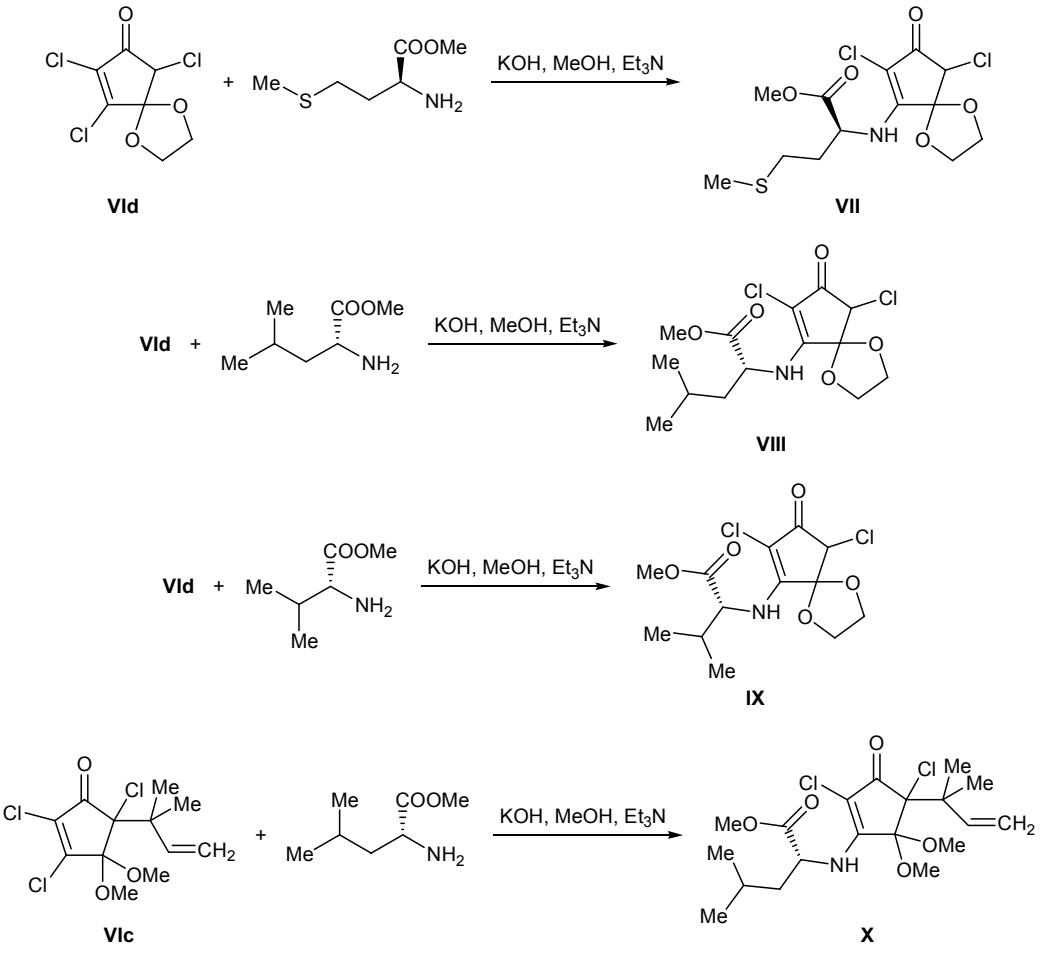
V



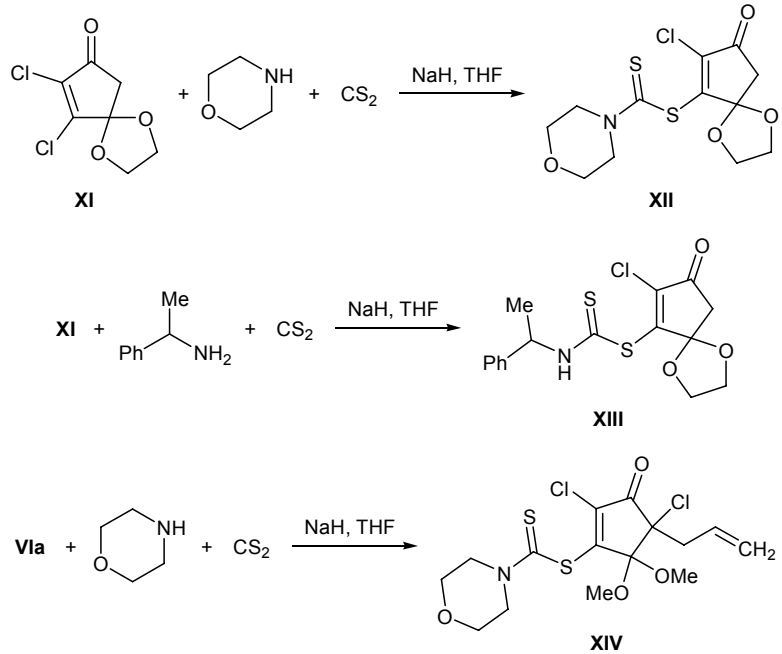
VIa–VId

R = CH_2=$CHCH_2$, R′ = Me (**a**); R = CH_2=C=CH, R′ = Me (**b**); R = CH_2=$CHCMe_2$, R′ = Me (**c**); R = H, R′R′ = CH_2CH_2 (**d**).

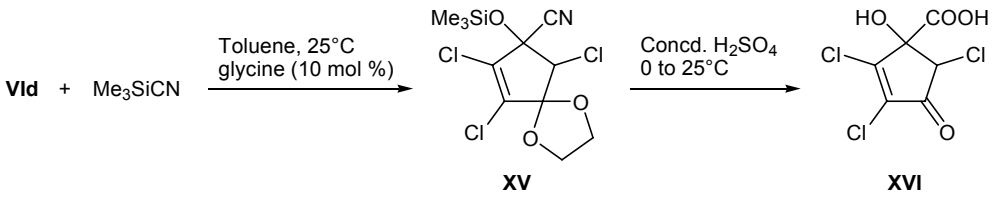
Scheme 1.



Scheme 2.



Scheme 3.



starting compounds we selected trichlorocyclopentenone derivatives **VI** which were synthesized by us previously [7] from hexachlorocyclopentadiene. Compounds **VIa**–**VId** are convenient substrates for further functionalization. Our search in this direction was substantiated by the fact that compounds **III** and **IV** obtained from chlorocyclopentenones **VIa** and **VIb** exhibited antiviral activity. For example, compound **III** showed a strong activity against tobacco mosaic viruses [8], whereas compound **IV** was highly active against H_1N_1 viruses.

Therefore, we performed functionalization of ring carbon centers in some trichlorocyclopentenones **VI** and their derivatives with a view to reveal signatures responsible for biological activity. The results thus obtained will be taken into account in the design of particular structures. Following the procedures described previously for compounds **IV** and **V** [9], we synthesized derivatives **VII**–**X** that are new conjugates of trichlorocyclopentenones **VIc** and **VId** with L-methionine, D-leucine, and D-valine (Scheme 1). By reactions of chlorocyclopentenones **XI** and **VIa** with sodium carbamodithioates generated *in situ* from carbon disulfide and amines (morpholine, α-methylbenzylamine) by the action of NaH we obtained new dithiocarbamate derivatives **XII**–**XIV** (Scheme 2).

In order to introduce a carboxy or amino functionality into chlorocyclopentenones **VI** we examined the reaction of compound **VId** with trimethylsilyl cyanide. The reaction smoothly occurred in toluene at 25°C in the presence of glycine as catalyst and afforded α-siloxy nitrile **XV** which was converted into trichlorocyclopentenone **XVI** by acid hydrolysis (Scheme 3).

EXPERIMENTAL

The IR spectra were recorded on Specord M-80 and Shimadzu IR Prestige-21 spectrometers from samples prepared as thin films or dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively, from solutions in $CDCl_3$ using tetramethylsilane as internal reference. The mass spectra (atmospheric pressure chemical ionization) were obtained on a Shimadzu LCMS-2010 instrument. The progress of reactions was monitored by TLC on Silufol and Sorbfil plates; spots were detected by calcination or by treatment with an alkaline solution of potassium permanganate. The products were isolated by column chromatography on silica gel (30–60 g of sorbent per gram of substrate); freshly distilled solvents were used as eluents.

***N*-(7,9-Dichloro-8-oxo-1,4-dioxaspiro[4.4]non-6-en-6-yl)-L-methionine methyl ester (VII).** A solution of 0.29 g (1.43 mmol) of L-methionine methyl ester hydrochloride in 5 ml of methanol, 0.08 g (1.43 mmol) of potassium hydroxide, and 0.11 ml (0.82 mmol) of triethylamine were added under stirring to a solution of 0.2 g (0.82 mmol) of ketone **VId** in 5 ml of methanol. The mixture was stirred until the initial compound disappeared (TLC) and evaporated, and the aqueous phase was acidified with 1 N hydrochloric acid to pH 4 and extracted with chloroform (4×10 ml). The extracts were combined, washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was subjected to chromatography on silica gel using ethyl acetate–petroleum ether (1:10) as eluent. Yield 0.25 g (84%), yellowish oily substance. IR spectrum, ν, cm^{-1}: 3292, 3280, 2954, 2920, 1730, 1699, 1604, 1527, 1425, 1290, 1271, 1211, 1168, 1124, 1028, 999, 968, 949, 878, 813, 714, 669, 543. ^1H NMR spectrum, δ, ppm: 2.08 s (3H, SMe), 2.12 m (2H, CH_2), 2.55 t (2H, SCH_2, J = 7.8 Hz), 3.77 s (3H, CO_2Me), 4.15–4.30 m (5H, OCH_2CH_2O, NCH), 4.34 s (1H, CHCl), 6.07 d (1H, NH, J = 8.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.05 (SMe), 29.47 (CH_2), 31.73 (SCH_2), 52.66 (CO_2**Me**), 54.49 (CHN), 66.15 (OCH_2), 61.74 (CHCl), 106.57 ($C^{5'}$), 106.62 ($C^{7'}$), 158.41 ($C^{6'}$), 171.29 (**C**O_2Me), 184.50 ($C^{8'}$). Found, %: C 41.86; H 4.53; Cl 19.95; N 4.01; S 8.79. $C_{13}H_{17}Cl_2NO_5S$. Calculated, %: C 42.17; H 4.63; Cl 19.15; N 3.78; S 8.66.

Compounds **VIII**–**X** were synthesized in a similar way.

***N*-(7,9-Dichloro-8-oxo-1,4-dioxaspiro[4.4]non-6-en-6-yl)-D-leucine methyl ester (VIII)** was synthesized from 0.2 g (0.82 mmol) of ketone **VId** and 0.26 g (1.43 mmol) of D-leucine methyl ester hydrochloride. Yield 0.16 g (55%). IR spectrum, ν, cm^{-1}: 3350, 3310, 2951, 1734, 1710, 1611, 1437, 1406, 1211, 1166, 1124, 1037, 991, 706, 699, 617. ^{1}H NMR spectrum, δ, ppm: 0.88 d (3H, CH_3, J = 6.0 Hz), 0.91 d (3H, CH_3, J = 7.5 Hz), 1.66 m (3H, CH, CH_2), 3.71 s (3H, CO_2Me), 4.14–4.31 m (5H, NCH, OCH_2CH_2O), 4.38 s (1H, CHCl), 5.76 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.35 (Me), 24.48 (CH), 41.91 (CH_2), 52.44 (CO_2**Me**), 54.22 (NCH), 61.86 (CHCl), 66.64 (OCH_2CH_2O), 106.73 ($C^{7'}$, $C^{5'}$), 158.19 ($C^{6'}$), 172.17 (**C**O_2Me), 184.0 ($C^{8'}$). Found, %: C 47.25; H 5.55; Cl 20.66; N 4.20. $C_{14}H_{19}Cl_2NO_5$. Calculated, %: C 47.74; H 5.44; Cl 20.13; N 3.98.

***N*-(7,9-Dichloro-8-oxo-1,4-dioxaspiro[4.4]non-6-en-6-yl)-D-valine methyl ester (IX)** was synthesized from 0.2 g (0.82 mmol) of ketone **VId** and 0.23 g (1.43 mmol) of D-valine methyl ester hydrochloride. Yield 0.08 g (~30%). IR spectrum, ν, cm^{-1}: 3309, 2963, 1739, 1715, 1616, 1265, 1209, 1146, 1030, 999, 949, 874, 810, 712. ^{1}H NMR spectrum, δ, ppm: 0.98 d (3H, CH_3, J = 7.6 Hz), 1.03 d (3H, CH_3, J = 7.8 Hz), 2.17 m (1H, CH), 3.75 m (1H, NCH), 3.79 s (3H, CO_2Me), 4.22–4.34 m (4H, OCH_2CH_2O), 4.37 s (1H, CHCl), 5.72 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.06 (Me), 29.67 (CH), 52.58 (CO_2**Me**), 60.29 (CHCl), 61.50 (NCH), 66.39 (OCH_2CH_2O), 107.09 ($C^{5'}$), 133.40 ($C^{7'}$), 150.45 ($C^{6'}$), 171.24 (**C**O_2Me), 182.44 ($C^{8'}$). Found, %: C 46.77; H 5.41; Cl 21.56; N 4.32. $C_{13}H_{17}Cl_2NO_5$. Calculated, %: C 46.17; H 5.07; Cl 20.97; N 4.14.

***N*-[2,4-Dichloro-4-(1,1-dimethylprop-2-en-1-yl)-5,5-dimethoxy-3-oxocyclopent-1-en-1-yl]-D-leucine methyl ester (X)** was synthesized as a 3:1 mixture of diastereoisomers (according to the ^{1}H NMR data) from 0.2 g (0.64 mmol) of allyl ketone **VIc** and 0.2 g (1.11 mmol) of D-leucine methyl ester hydrochloride. Yield 0.145 g (54%). IR spectrum, ν, cm^{-1}: 3292, 2960, 1744, 1705, 1589, 1522, 1377, 1247, 1207, 1178, 1149, 1082, 1064, 1024, 924, 820, 746, 721. ^{1}H NMR spectrum, δ, ppm: 0.97 d (3H, CH_3, J = 6.0 Hz), 1.01 d (3H, CH_3, J = 6.0 Hz), 1.19 s and 1.26 s (6H, CH_3), 1.66 m (1H, CH), 1.74 m (2H, CH_2), 3.33 s (3.24) and 3.49 s (3.46) (6H, OMe), 3.79 s (3H, CO_2Me), 4.99–5.04 m (3H, =CH_2, NCH), 5.76 d (1H, NH, J = 8.6 Hz), 6.07 d.d (1H, =CH, J = 10.5, 17.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.80 and 22.64 (CH_3), 24.17 (24.31) (CH), 24.68 (24.80) and 25.23 (25.12) (CH_3), 42.35 (43.40) ($C^{1''}$), 45.44 (45.32) (CH_2), 52.51 (52.31) and 52.73 (OMe), 53.68 (53.43) (CO_2**Me**), 54.02 (CH), 84.62 ($C^{4'}$), 99.69 ($C^{2'}$), 101.94 ($C^{5'}$), 112.80 (112.59) (=CH_2), 143.31 (143.41) (=CH), 158.70 ($C^{1'}$), 172.56 (**C**O_2Me), 187.35 (C=O). Mass spectrum: m/z 422 (I_{rel} = 100%) $[M + H]^+$.

7-Chloro-8-oxa-1,4-dioxaspiro[4.4]non-6-en-6-yl morpholine-4-carbodithioate (XII). A solution of 0.12 ml (1.44 mmol) of morpholine in 3 ml of anhydrous THF was added under stirring at room temperature to a suspension of 0.07 g (1.44 mmol) of sodium hydride (preliminarily washed with anhydrous hexane) in 5 ml of anhydrous THF. The mixture was stirred for 30 min, 0.09 ml (1.44 mmol) of carbon disulfide was added, the mixture was stirred for 20 min, 0.20 g (0.96 mmol) of compound **XI** was added, and the mixture was stirred at room temperature until the initial compound disappeared (TLC). The mixture was quenched by adding a required amount of a saturated solution of ammonium chloride and evaporated, the residue was dissolved in chloroform, the solution was filtered through a thin layer of silica gel, and the filtrate was evaporated. Yield 0.29 g (91%). ^{1}H NMR spectrum, δ, ppm: 2.82 s (2H, CH_2), 3.72 s (4H, OCH_2CH_2O), 4.01 m (4H, CH_2N), 4.14 m (4H, OCH_2). ^{13}C NMR spectrum, δ_C, ppm: 65.89 (OCH_2CH_2O), 109.83 ($C^{5'}$), 143.13 ($C^{7'}$), 157.06 ($C^{6'}$), 185.36 (C=O), 193.01 (C=S). Mass spectrum, m/z (I_{rel}, %): 336 $[M + H]^+$, 293, 279.

Compounds **XIII** and **XIV** were synthesized in a similar way.

7-Chloro-8-oxo-1,4-dioxaspiro[4.4]non-6-en-6-yl (1-phenylethyl)dithiocarbamate (XIII) was synthesized from 0.2 g (0.96 mmol) of compound **XI**, 0.14 g (1.15 mmol) of α-methylbenzylamine, 0.07 g (1.44 mmol) of NaH, and 0.09 ml (1.44 mmol) of CS_2. Yield 0.31 g (89%). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.61 d (3H, CH_3, J = 6.85 Hz), 2.62 s (2H, CH_2), 4.03 m and 4.44 m (2H each, OCH_2CH_2O), 4.99 q (1H, CH, J = 6.84 Hz), 7.23 m (1H, NH), 7.33 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 25.06 (CH_3), 47.76 (CH_2), 58.23 (CH), 67.30 (OCH_2CH_2O), 111.53 ($C^{5'}$); 126.46, 127.08, 129.15, 129.45, 129.88, 141.99 (C_{arom}); 144.99 ($C^{7'}$), 153.50 ($C^{6'}$), 195.81 (C=O), 199.45 (C=S). Found, %: C 51.43; H 4.43; Cl 9.95; N 4.0; S 17.89. $C_{16}H_{16}ClNO_3S_2$. Calculated, %: C 51.95; H 4.36; Cl 9.58; N 3.79; S 17.34.

4-Allyl-2,4-dichloro-5,5-dimethoxy-3-oxocyclopent-1-en-1-yl morpholine-4-carbodithioate (XIV) was synthesized from 0.2 g (0.70 mmol) of compound

VIa, 0.06 g (1.05 mmol) of NaH, 0.07 ml (1.05 mmol) of CS_2, and 0.09 ml (1.05 mmol) of morpholine. Yield 0.23 g (80%). IR spectrum, ν, cm^{-1}: 2947, 2922, 2854, 2717, 2461, 2360, 2332, 1732, 1719, 1674, 1431, 1269, 1230, 1211, 1188, 1149, 1115, 1070, 1018, 974, 926, 910, 874, 820, 714, 681. ^{1}H NMR spectrum, δ, ppm: 2.81 d.d (1H, CH_2, J = 7.3, 15.1 Hz) and 3.16 d.d (1H, CH_2, J = 6.9, 15.1 Hz), 3.42 s (3H, OCH_3), 3.59 s (3H, OCH_3), 3.81 t (4H, CH_2N, J = 4.6 Hz), 4.17 m (4H, OCH_2), 5.17 m (2H, $=CH_2$), 5.84–5.96 m (1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 40.84 (CH_2), 43.09 (NCH_2), 52.10 (OCH_3), 63.67 ($C^{4'}$), 66.19 (OCH_2), 104.37 ($C^{5'}$), 119.83 ($=CH_2$), 130.91 ($C^{2'}$), 157.0 ($C^{1'}$), 131.54 (=CH), 184.68 (C=O), 189.50 (C=S). Found, %: C 43.37; H 4.45; Cl 17.85; N 3.46; S 15.94. $C_{15}H_{19}Cl_2NO_4S_2$. Calculated, %: C 43.69; H 4.64; Cl 17.20; N 3.40; S 15.55.

6,8,9-Trichloro-7-trimethylsiloxy-1,4-dioxaspiro-[4.4]non-8-ene-7-carbonitrile (XV). Ketone **VId**, 0.2 g (0.82 mmol), was dissolved in 5 ml of toluene, 0.01 g (0.08 mmol) of glycine and 0.122 g (1.23 mmol) of trimethylsilyl cyanide were added, and the mixture was stirred for 24 h at room temperature. The mixture was then filtered through a layer of silica gel, the sorbent was washed with methylene chloride, and the solution was evaporated. Yield 0.26 g (95%). IR spectrum, ν, cm^{-1}: 3325, 2960, 1635, 1458, 1377, 1260, 1246, 1217, 1180, 1155, 1130, 1109, 1059, 1031, 953, 920, 874, 846, 808, 758, 718, 690, 638, 570. Mass spectrum, m/z (I_{rel}, %): 243 (28) $[M + H - Me_3SiCN]^+$, 232 (100) $[M + H - Me_3Si - Cl]^+$. Major stereoisomer: ^{1}H NMR spectrum, δ, ppm: 0.34 s (9H, $SiCH_3$), 4.17–4.24 m (4H, OCH_2CH_2O), 4.26 s (1H, CHCl). ^{13}C NMR spectrum, δ_C, ppm: 1.06 (SiMe), 66.74 and 67.42 (OCH_2CH_2O), 67.92 (CHCl), 74.84 (C^7), 110.31 (C^5), 116.41 (CH), 132.29 (C^8), 136.62 (C^9); minor stereoisomer: ^{1}H NMR spectrum, δ, ppm: 0.35 s (9H, $SiCH_3$), 4.17–4.24 m (4H, OCH_2CH_2O), 4.58 s (1H, CHCl). ^{13}C NMR spectrum, δ_C, ppm: 1.06 (SiMe), 67.09 and 67.35 (OCH_2CH_2O), 69.23 (CHCl), 78.10 (C^7), 108.81 (C^5), 114.64 (CH), 133.69 (C^8), 135.33 (C^9).

2,3,5-Trichloro-1-hydroxy-4-oxocyclopent-2-ene-1-carboxylic acid (XVI). Compound **XV**, 0.1 g (0.291 mmol), was added in portions under stirring to 3 ml of concentrated sulfuric acid cooled to 0°C. The mixture was stirred for 1 h at 0°C, allowed to warm up to room temperature, and treated with chloroform (3 × 5 ml). The extracts were combined, dried over $MgSO_4$, and evaporated, and the residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1:10) as eluent. Yield 0.033 g (~50%). IR spectrum, ν, cm^{-1}: 3462, 2993, 1737, 1693, 1682, 1597, 1573, 1244, 1203, 1170, 1124, 1010, 985, 926, 841, 827, 727. ^{1}H NMR spectrum: δ 5.14 ppm, s (1H, CHCl). ^{13}C NMR spectrum, δ_C, ppm: 61.41 (CHCl), 79.72 (C^1), 132.67 and 159.44 (C^2, C^3), 169.49 (CO_2H), 188.12 (C^4). Found, %: C 28.88; H 0.86; Cl 43.93. $C_6H_3Cl_3O_4$. Calculated, %: C 29.36; H 1.23; Cl 43.33.

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