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Prostanoids: LXXIX.* Analogs of "Marine" Prostanoids. 14,15-Dihydro-11-chlorochlorvulone II**

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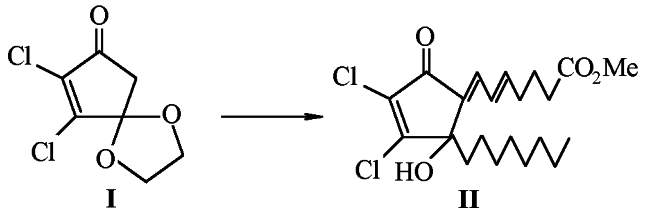
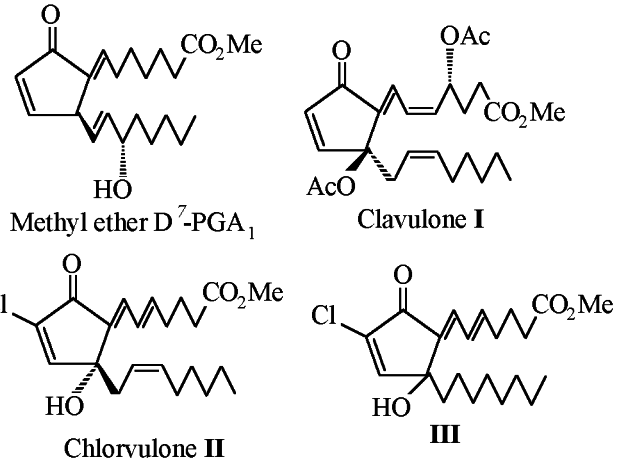
Abstract—(±)-14,15-dihydro-11-chlorochlorvulone was synthesized starting with 1,4-dioxa-6,7-dichlorospiro[4.4]non-6-ene.

In extension of our studies on application of the functionalized cyclopentenone (**I**) [2] to the synthesis of prostaglandins (PG) [3–5] we report here on results demonstrating "internal synthetic potential" of the basic synthon by an example of performed efficient transition **I** → **II**.



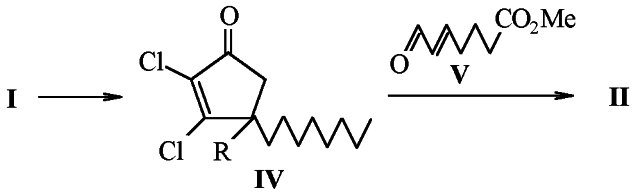
As to the selection of compound **II** for the object of the synthesis we should like to mention, that the possible application in medicine of the alkylidenecyclopentene prostaglandins, among them also compound **II**, is antitumor therapy. For instance, the methyl ether Δ^7-PGE_1 is now subjected to preliminary tests for chemotherapy of ovary cancer [6]; high antiproliferative properties possess representatives of "marine prostanoids", clavulones, chlorvulones, punaglandins [7], and their analogs, e.g., compound **III** [8].

This activity is provided by the part of the molecule containing the cross-conjugated alkylidenecyclopentenone system; in the "marine" PG are also important the C^{12} center with a tertiary alcohol group, and chlorine atom attached to C^{10} [6, 7]. As seen from the structure the target compound **II** contains two chlorine atoms, and that obviously enhances the properties of its enone system as Michael acceptor.*** Besides the labile Cl at C^{11} atom can be easily replaced by nucleophilic groups, i.e., arises a possibility to influence the reactivity of the enone system.



A possible path of preparation of compound **II** from the initial ketal **I** is shown in Scheme 1. The key stage consists in transformation of enone **IV** into enolate and condensation of the latter with aldehydo-

Scheme 1.



* For preceding communication, see [1].

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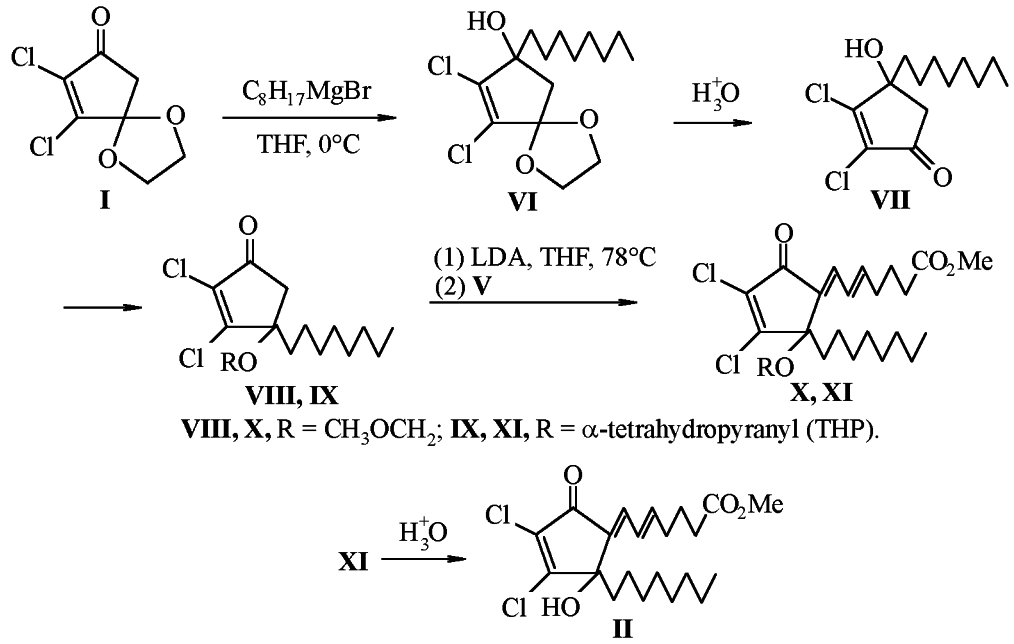
*** Antiproliferative properties of the alkylidenecyclopentenone PG are due to their capability for formation of covalent bonds with NH_2 and SH groups of biological systems along the route of conjugate 1,4-addition and to inhibiting the synthesis of macromolecules: proteins, DNA, etc.

Scheme 2.



VIII, X, R = CH_3OCH_2; **IX, XI,** R = α-tetrahydropyranyl (THP).

ester **V** [9]. Although this strategy in the synthesis of chlorvulones and clavulones was successfully used [10–12], somewhat dubious seemed the possibility to obtain enolate from protected derivatives of the highly reactive compound **IV**.

We planned to introduce an octyl group into the ketal of cyclopentenedione (**I**) with simultaneous building up of a center with a tertiary alcohol group in compound **IV** by condensation of the initial ketone with octylmagnesium bromide (Scheme 2). The experiments showed the absence of products originating from hydride reduction and revealed a clean addition of the organomagnesium reagent to the keto group of compound **I**. Tertiary alcohol **VI** was obtained in 73% yield. The subsequent acid hydrolysis of ketal **VI** afforded enone **VII** in 82% yield. Prior to the key stage of aldol condensation alcohol **VII** was converted into methoxymethyl (**VIII**) and tetrahydropyranyl (**IX**) ethers. The enolates were generated therefrom by treatment with lithium diisopropylamide (LDA). The reaction of the intermediate enolates with aldehydoether **V** occurred cleanly furnishing in both cases directly 5*E*,7*E*-trienones **X** and **XI** in over 70% yield. The corresponding 7*Z*-derivatives **X** and **XI** arise in small quantities (~5%). The 5*E*,7*E*-configuration of the conjugated double bonds system is proved by the presence in their ^{1}H NMR spectra of a downfield doublet signal of H^7 t 7.10 ppm ($J_{6,7}$ ~12 Hz) [13–15]. The acid hydrolysis failed to deprotect methoxymethyl ether **X**, but the tetrahydropyranyl ether (**IX**) was sufficiently labile, and after purification by column chromatography on silica gel we isolated the target compound **II** in 62% yield.

Thus the investigation demonstrated that dichloroderivative **I** that is easily prepared from hexachlorocyclopentadiene is a convenient initial compound for building up the structure of new pharmacologically promising 11-chlorochlorvulones.

EXPERIMENTAL

IR spectra were obtained on spectrophotometer UR-20 from thin film or mull in mineral oil. ^{1}H and ^{13}C NMR spectra were registered from solutions in $CDCl_3$ on Bruker AM-300 spectrometer at operating frequencies 300 and 75.47 MHz respectively, internal reference TMS.

8-Hydroxy-1,4-dioxa-8-octyl-6,7-dichlorospiro-[4.4]non-6-ene (VI). To a stirred solution of 0.42 g (2 mmol) of enone **I** in 10 ml of anhydrous THF under argon at −20°C was added dropwise 8 ml of 0.5 N solution of $C_8H_{17}MgBr$ in THF. The reaction mixture was warmed to 0°C and stirred at this temperature for 0.5 h more. Then 10 ml of saturated aqueous solution of NH_4Cl was added, the reaction product was extracted into ether, the combined extracts were dried on Na_2SO_4 and evaporated. The residue was subjected to chromatography on SiO_2 to afford 0.38 g (73%) of oily alcohol **VI**. IR spectrum,

ν, cm^{-1}: 3330, 1650. ^1H NMR spectrum, δ, ppm: 0.85 t (3H, CH_3, *J* 7 Hz), 1.00–2.00 m (14H, $7CH_2$), 2.15 d (1H, H^9, *J* 14.3 Hz), 2.40 d (1H, H^9, *J* 14.3 Hz), 3.90–4.20 m (4H, $2CH_2O$). ^{13}C NMR spectrum, δ_C, ppm: 13.77 (Me), 20.40 ($C^{2'}$), 23.22 ($C^{3'}$), 28.85 ($C^{5'}$), 29.28 ($C^{4'}$), 29.51 ($C^{7'}$), 31.64 ($C^{6'}$), 37.72 ($C^{1'}$), 48.02 (C^9), 65.71 (CH_2O), 65.80 (CH_2O), 79.30 (C^4), 112.15 (C^5), 131.39 (C^7), 139.91 (C^6).

4-Hydroxy-4-octyl-2,3-dichlorocyclopent-2-en-1-one (VII). A solution of 0.65 g (2 mmol) of ketal **VI** in 10 ml of acetone and 0.2 ml 15% HCl was refluxed for 1 h, cooled to room temperature, 2 ml of saturated water NaCl solution was added, and the product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were washed with saturated water solution of NaCl till neutral, dried with $MgSO_4$, filtered, and evaporated. We obtained 0.46 g of oily ketone (**VII**). IR spectrum, ν, cm^{-1}: 3450, 1730, 1650, 1615. ^1H NMR spectrum, δ, ppm: 0.75 t (3H, CH_3, *J* 7 Hz), 1.00–1.30 m (14H, $7CH_2$), 2.58 d (1H, H^5, *J* 18.6 Hz), 2.74 d (1H, H^5, *J* 18.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.77 (Me), 22.31 ($C^{7'}$), 23.48 ($C^{2'}$), 28.89 ($C^{3'}$), 29.03 ($C^{4'}$), 29.43 ($C^{5'}$), 31.48 ($C^{6'}$), 37.54 ($C^{1'}$), 47.13 (C^5), 77.49 (C^4), 132.20 (C^2), 166.83 (C^3), 194.30 (C=O). Found, %: C 55.80; H 6.80; Cl 25.15. $C_{13}H_{20}Cl_2O_2$. Calculated, %: C 55.92; H 6.73; Cl 25.40.

2,3-Dichloro-4-methoxymethoxy-4-octylcyclopent-2-en-1-one (VIII). To a stirred solution of 0.43 g (1.54 mmol) of alcohol **VII** and 0.24 g (3 mmol) of chloromethyl ether in 10 ml of anhydrous dichloroethane at 20°C was added 0.39 g (3 mmol) of freshly distilled diisopropylethylamine. The reaction mixture was stirred for 3 h at 55°C, then cooled to 20°C, diluted with 40 ml of CH_2Cl_2, washed with saturated aqueous NaCl solution till neutral, dried on Mg$$O_4$, filtered, and evaporated. We obtained 0.46 g (92%) of compound **VIII**. IR spectrum, ν, cm^{-1}: 1750, 1640, 1610. ^1H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, *J* 7 Hz), 1.10–2.20 m (14H, $7CH_2$), 2.72 d (1H, H^5, *J* 18.7 Hz), 3.12 d (1H, H^5, *J* 18.7 Hz), 3.36 s (3H, OMe), 4.65 m (2H, OCH_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.73 (Me), 22.41 ($C^{7'}$), 23.21 ($C^{2'}$), 28.61 ($C^{3'}$) 28.96 ($C^{4'}$), 29.51 ($C^{5'}$), 31.64 ($C^{6'}$), 37.48 ($C^{1'}$), 44.09 (C^5), 55.47 (OMe), 82.57 (C^4), 92.16 (OCH_2O), 134.91 (C^2), 163.00 (C^3), 192.29 (C=O).

2,3-Dichloro-4-octyl-4-(2-tetrahydropyranyloxy)-cyclopent-2-en-1-one (IX). To a stirred solution of 0.43 g (1.54 mmol) of alcohol **VII** and 0.01 g of toluenesulfonic acid in 10 ml of CH_2Cl_2 at 0°C was added 0.14 g (1.67 mmol) of freshly distilled 2,3-dihydropyran. The reaction mixture was stirred for 30 min, 0.05 g of fine powder of $NaHCO_3$ was added, the mixture was stirred for 10 min, filtered, and the filtrate was evaporated. We obtained 0.5 g (93%) of oily compound **X** as a mixture of diastereomers in 3 : 1 ratio (^1H NMR data). IR spectrum, ν, cm^{-1}: 1740, 1650, 1610. ^1H NMR spectrum, δ, ppm: 0.78 t (3H, CH_3, *J* 7.0 Hz), 1.10–2.00 m (22H, $11CH_2$), 2.60 d and 3.35 d (1.5H, C^5H_2, main diastereomer, *J* 18.7 Hz), 2.63 d and 2.78 d (0.5H, C^5H_2, minor diastereomer, *J* 18.7 Hz), 3.30–3.40 m (1H, CH_2O), 3.80 m (1H, CH_2O), 4.40 m (0.75H, $C^{1'}H$) and 4.60 m (0.25H, $C^{1'}H$).

Main diastereomer (IX). ^{13}C NMR spectrum, δ_C, ppm: 13.96 (Me), 19.79 ($C^{3''}$), 22.50 ($C^{7'}$), 23.22 ($C^{4''}$), 24.96 ($C^{2'}$), 29.04 ($C^{3'}$), 29.19 ($C^{4'}$), 29.50 ($C^{5'}$), 31.52 ($C^{2''}$), 31.67 ($C^{6'}$), 38.04 ($C^{1'}$), 44.23 (C^5), 62.98 ($C^{5''}$), 82.88 (C^4), 95.48 ($C^{1''}$), 135.01 (C^2), 165.38 (C^3), 193.41 (C=O).

Minor diastereomer (IX). ^{13}C NMR spectrum, δ_C, ppm: 13.96 (Me), 19.56 ($C^{3''}$), 22.50 ($C^{7'}$), 23.22 ($C^{4''}$), 24.96 ($C^{2'}$), 29.04 ($C^{3'}$), 29.19 ($C^{4'}$), 29.50 ($C^{5'}$), 31.18 ($C^{2''}$), 31.67 ($C^{6'}$), 36.39 ($C^{1'}$), 43.80 (C^5), 63.04 ($C^{5''}$), 81.69 (C^4), 94.16 ($C^{1''}$), 133.54 (C^2), 165.73 (C^3), 193.41 (C=O).

14,15-Dihydro-12-methoxymethoxy-11-chloro-chlorvulone II (X). To a solution of 0.12 g (1.2 mmol) of i-Pr_2NH in 5 ml of anhydrous THF cooled to –10°C under argon was added dropwise 2.4 ml of 0.5 N solution of BuLi in hexane. The reaction mixture was stirred for 15 min, and dropwise was added a solution of 0.32 g (1.2 mmol) of ketone **X** in 2 ml of THF. Then the reaction mixture was cooled to –78°C, and a solution of 0.19 g (1.2 mmol) of aldehyde V in 3 ml of THF was added thereto. The reaction mixture was stirred for 20 min at –78°C and 30 min at –20°C, then kept for 30 min at room temperature Afterwards 2 ml of 1N HCl was added, the mixture was stirred for 10 min, and the products were extracted into ethyl acetate (3 × 30 ml). The combined extracts were washed with water till neutral, dried with $MgSO_4$, and evaporated. We obtained 0.4 g of crude reaction product that was purified by chromatography on SiO_2 (eluent pentane–ethyl acetate, 7 : 3). We isolated 0.29 g (73%) of oily compound **X**. IR spectrum, ν, cm^{-1}: 3450, 1740, 1640. ^1H NMR spectrum, δ, ppm: 0.84 t (3H, CH_3, *J* 7 Hz), 1.05–1.35 m (10H, $5CH_2$), 1.75–2.40 m (10H, $5CH_2$), 3.33 s (3H, OMe), 3.66 s (3H, OMe), 4.35 d (1H, OCH_2O, *J* 7.0 Hz), 4.45 d (1H, OCH_2O,

J 7.0 Hz), 6.30 d.t (1H, H^5, *J* 7.0, 15.1 Hz), 6.52 d.d (1H, H^6, *J* 12.0, 15.1 Hz), 7.10 d (1H, H^7, *J* 12.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.93 (Me), 22.49 (C^{19}), 23.59 (C^{14}), 24.63 (C^3), 28.96 (C^{15}), 29.46 (C^{16}), 29.62 (C^{17}), 31.62 (C^{18}), 32.89 (C^4), 33.09 (C^2), 36.24 (C^{13}), 51.43 (OMe), 83.90 (C^{12}), 125.47 (C^5), 134.50 (C^6), 135.50 (C^2), 137.33 (C^5), 149.06 (C^7), 161.75 (C^3), 173.24 (CO_2), 184.48 (C=O).

14,15-Dihydro-12-(2-tetrahydropyranyloxy)-11-chlorochlorvulone II (XI) was obtained by procedure similar to that described for compound **X** by condensation of enolate of ketone **IX** with aldehyde **V**. Yield of oily compound **XI** 65%. IR spectrum, ν, cm^{-1}: 1740, 1640. ^1H NMR spectrum, δ, ppm: 0.84 t (3H, CH_3, *J* 7 Hz), 1.05–1.35 m (10H, $5CH_2$), 1.10–2.50 m (26H, $13CH_2$), 3.60 s (3H, OMe), 4.45 br.s and 4.75 br.s (1H, OCHO), 6.25 m (1H, H^5), 6.60 m (1H, H^6), 7.10 d (1H, H^7, *J* 11.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.52 and 13.54 (Me), 19.32 and 19.45 ($C^{3'}$), 22.48 and 22.91 (C^{19}), 23.56 and 23.65 (C^{14}), 24.63 and 25.10 ($C^{4'}$), 24.96 and 25.09 (C^3), 28.93 and 29.12 (C^{15}), 29.21 and 29.31 (C^{16}), 29.31 and 29.54 (C^{17}), 30.91 and 31.12 ($C^{2'}$), 31.62 and 31.70 (C^{18}), 32.51 and 32.60 (C^4), 32.88 and 32.96 (C^2), 36.09 and 38.73 (C^{13}), 51.61 (OMe), 61.55 and 62.78 ($C^{5'}$), 84.19 and 84.33 (C^{12}), 94.61 and 95.13 ($C^{1'}$), 125.12 and 125.50 (C^5), 133.95 and 135.03 (C^6), 133.44 and 136.59 (C^{10}), 137.68 and 138.40 (C^8), 147.24 and 148.69 (C^7), 158.59 and 161.97 (C^{11}), 173.30 and 173.41 (C^1), 184.37 and 184.44 (C=O).

14,15-Dihydro-11-chlorochlorvulone II (II). A solution of 0.25 g (0.05 mmol) of ether **XI** in 10 ml of acetone and 0.2 ml of 15% HCl was stirred at room temperature for 2 h, then to the reaction mixture was added 2 ml of saturated water solution of NaCl, and the products were extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were washed with saturated water NaCl solution till neutral, dried with $MgSO_4$, filtered, evaporated, the residue was subjected to chromatography on SiO_2. We isolated 0.13 g (62%) of oily compound **II**. IR spectrum, ν, cm^{-1}: 3450, 1740, 1640. UV spectrum, λ_{max}^{EtOH}, nm: 241 (ε 10200), 314 (ε 10000). ^1H NMR spectrum, δ, ppm: 0.84 t (3H, CH_3, *J* 7.0 Hz), 1.15–1.35 m (12H, $6CH_2$), 1.81 q (2H, CH_2, *J* 7.3 Hz), 2.06 m (2H, CH_2), 2.32 m (4H, $2CH_2$), 2.85 m (1H, OH), 3.66 s (3H, OMe), 6.25 d.t (1H, C^5H, *J* 7.0, 15.0 Hz), 6.70 t.d.d (1H, C^6H, *J* 15.0, 11.8, 1.3 Hz), 7.01 d (1H, C^7H, *J* 11.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.00 (C^{20}), 22.53 (C^{19}), 23.66 (C^{14}), 24.03 (C^3), 29.00 (C^{15}), 29.05 (C^{16}), 29.29 (C^{17}), 31.68 (C^{18}), 32.67 (C^4), 33.20 (C^2), 36.59 (C^{13}), 51.60 (OMe), 79.60 (C^{12}), 125.47 (C^5), 133.21 (C^8), 134.00 (C^{10}), 134.68 (C^6), 148.29 (C^7), 161.75 (C^{11}), 173.68 (CO_2), 184.48 (C=O).

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