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Prostanoids: LXXX.* Analogs of "Marine" Prostanoids. (±)-11-Chlorochlorvulone II**

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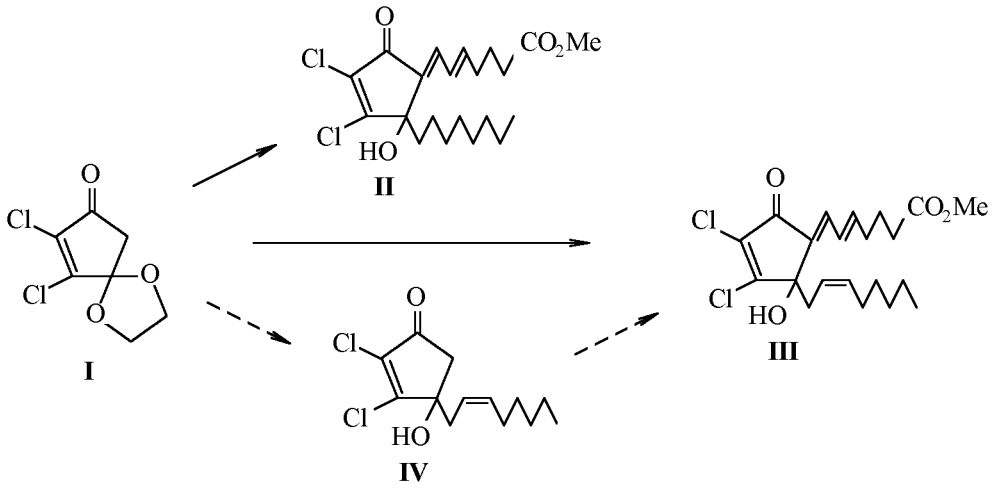
Abstract—Analog of chlorvulone II containing an extra chlorine atom at C^{11} was synthesized starting with 1,4-dioxa-6,7-dichlorospiro[4.4]non-6-ene.

In the preceding publication [1] we considered the pharmacological opportunities and described an efficient procedure for transformation of easily available dichlorocyclopentenone (**I**) [2] into 14,15-dihydro-11-chlorochlorvulone II (**II**) (chlorvulones are treated in [2, 3]). Here we report on the synthesis of 1-chlorochlorvulone II (**III**) from the same initial compound (Scheme 1).

The synthesis of previously described hydroxycyclopentenone (**IV**) [4] was carried out by more practical procedure. Both this process and the key transition (**IV** → **III**) are presented in Scheme 2. The building up of the side chain of compound **IV** was here performed proceeding from adduct **V** obtained in high yield by Reformatsky reaction from enone **I** and allylzinc bromide in DMF. Further stages of acid hydrolysis of the ketal function in adduct **V** and hydroxy group protection in hydroxyketone **VI** by conversion into methoxymethyl ether also occurred without complications and resulted in ketone **VII**. The reduction of ketone **VII** with borohydride afforded diastereomeric mixture of secondary alcohols **VIII** that was converted into ether **IX** by treatment with *t*-$BuMe_2SiCl$–ImH–DMF.

Periodate rupture of the terminal double bond in ether **IX** in the presence of OsO_4 furnished aldehyde **X** that was subjected to olefination by treatment with hexylidenetriphenylphosphonium ylide to afford *Z*-olefin **XI**. Successive deprotection of both groups in compound **XI** and oxidation of the diol **XII** obtained with Jones' reagent resulted in hydroxycyclopentenone **IV**. In the final stages of the synthesis tertiary alcohol **IV** was transformed into tetrahydropyranyl ether **XIII**, the latter was converted into

Scheme 1.



* For preceding communication, see [1].

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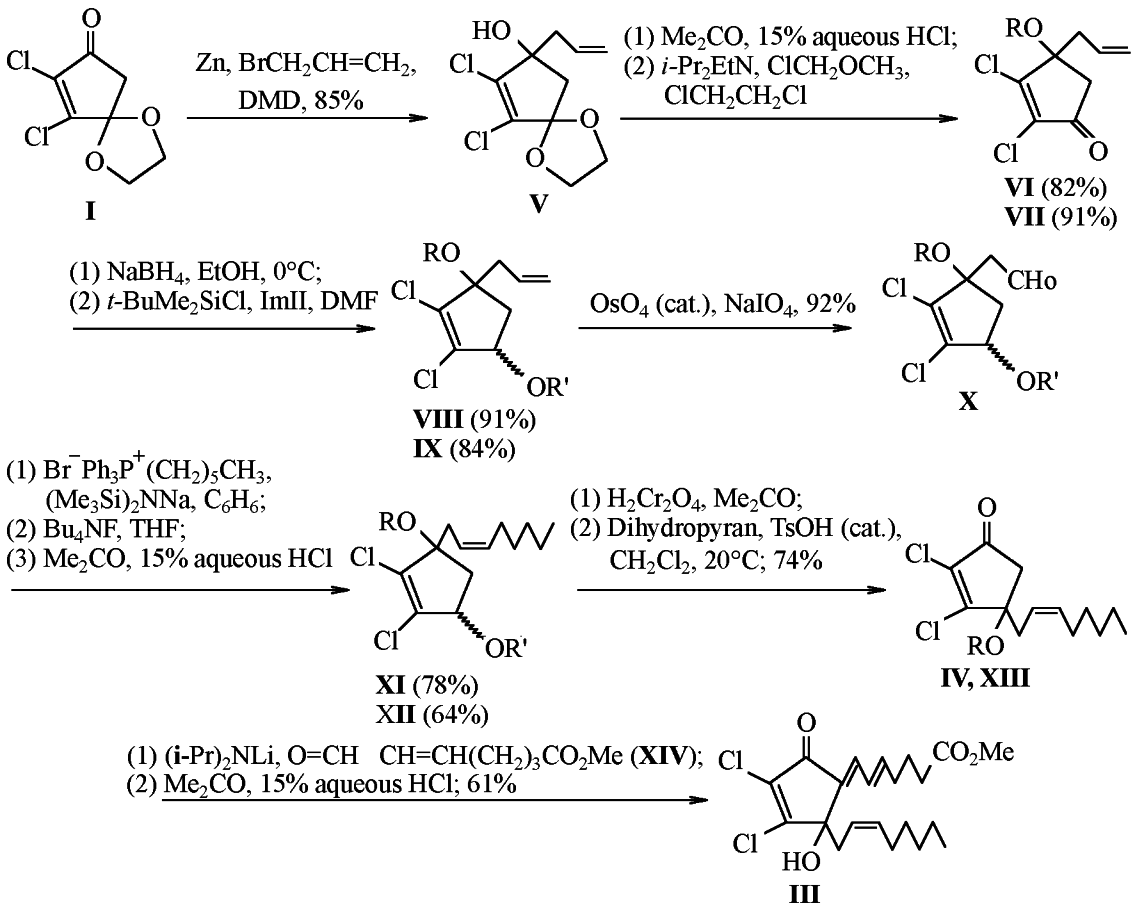
Scheme 2.



R = H (**IV, VI, XII**), CH_3OCH_2 (**VII, VIII, X, XI**), 2-tetrahydropyranyl (**XIII**); R' = H (**VIII, XII**), *t*-$BuMe_2Si$ (**IX**–**XI**).

enolate by the action of $(i\text{-Pr})_2NLi$, and the condensation of the enolate with α,β-unsaturated aldehydoether **XIV** [5] gave rise to a corresponding adduct of crotonic type that was subjected to acid hydrolysis without purification. After chromatography on a column packed with SiO_2 the overall yield of the target compound **III** with respect to ketoalcohol **IV** was over 60%. ^1H NMR spectrum of 11-chlorochlorvulone (**III**) synthesized was similar to that of the native prostanoid and is distinguished only by the lack of $C^{11}H$ signal. The 5*E*,7*E*-configuration of the double bonds system in compound **III** is proved by appearance of a downfield doublet from C^7H at 6.96 ppm, $J_{6,7}$ 11.8 Hz in the ^1H NMR spectrum [6–8].

EXPERIMENTAL

IR spectra were obtained on spectrophotometer UR-20 from samples prepared as thin film or mull in mineral oil. ^1H 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. UV spectra were recorded on spectrometer Specord M-400.

11-Chlorochlorvulone II (III). To a stirred solution of 0.33 g (1.2 mmol) of ketoalcohol **IV** and 0.01 g of *p*-toluenesulfonic acid in 20 ml of CH_2Cl_2 at 20°C was added 0.11 g (1.3 mmol) of freshly distilled 2,3-dihydropyran. The reaction mixture was stirred for 30 min, then 0.1 g of $NaHCO_3$ was added, the mixture was filtered, and evaporated to afford 0.43 g of compound **XIII**. IR spectrum of the tetrahydropyranyl derivative **XIII** showed the absence of a free OH group. To lithium diisopropylamide prepared in a separate flask (from 0.12 g of $i\text{-Pr}_2NH$ in 5 ml of anhydrous THF and 2.4 ml of 0.5 N solution of BuLi in hexane, Ar, 0°C, 20 min) was added dropwise at −10°C a solution of 0.43 g (1.2 mmol) of ketone **XIII** in 2 ml of THF. The mixture was kept at the same temperature for 30 min, then cooled to

–78°C, and a solution of 0.19 g (1.2 mmol) of aldehyde **XIV** in 3 ml was added thereto. The reaction mixture was stirred 20 min at –78°C and 30 min at –30°C, then was maintained for 30 min at room temperature, 2 ml of 1 N HCl was added, the mixture was stirred for 10 min, and the reaction product was extracted into ethyl acetate (3 × 30 ml). The combined extracts were washed with water till neutral, dried on $MgSO_4$, and evaporated. The residue obtained (0.4 g) was dissolved in 10 ml of acetone, 0.2 ml of 15% HCl solution was added, and the mixture was stirred for 2 h at 20°C. To the mixture was poured 2 ml of saturated aqueous NaCl solution, and the reaction product was extracted with EtOAc (3 × 10 ml). The combined organic extracts were washed with saturated aqueous NaCl solution till neutral, dried with $MgSO_4$, and evaporated , After chromatography of the residue on SiO_3 we obtained 0.3 g (61%) of oily alcohol **III**. IR spectrum (ν, cm^{-1}): 1640, 1740, 3450. UV spectrum (λ_{max}^{EtOH}, nm): 241 (ε 10400), 313 (ε 10000). ^1H NMR spectrum (δ, ppm): 0.85 t (3H, CH_3, *J* 7.0 Hz), 1.20 m (6H, $3CH_2$), 1.7 s (1H, OH), 1.77 quintet (2H, CH_2, *J* 7.3 Hz), 1.89 m (2H, CH_2, *J* 7.4 Hz), 2.32 m (4H, $2CH_2$), 2.83 d (2H, CH_2, *J* 7.7 Hz), 3.63 s (3H, OMe), 4.82 d.t (1H, $C^{14}H$, *J* 10.9, 7.7 Hz), 5.40 d.t.t (1H, $C^{15}H$, *J* 10.9, 7.4, 1.2 Hz), 6.26 d.t.t (1H, C^5H, *J* 15, 7.1, 0.8 Hz), 6.76 t.d.d (1H, C^6H, *J* 7.1, 15, 1.3 Hz), 6.96 d.d (1H, C^7H, *J* 11.8, 0.8 Hz). ^{13}C NMR spectrum (δ_C, ppm): 13.98 (C^{20}), 22.44 (C^{19}), 23.66 (C^3), 27.44 (C^{16}), 29.10 (C^{17}), 31.46 (C^{18}), 32.67 (C^4), 33.21 (C^2), 34.69 (C^{13}), 51.64 (OMe), 79.20 (C^{12}), 120.35 (C^{14}), 126.68 (C^6), 133.21 (C^8), 134.04 (C^{15}), 134.68 (C^{10}), 137.08 (C^7), 148.32 (C^5), 161.49 (C^{11}), 173.76 (CO_2), 184.42 (C=O). Found, %: C 60.52; H 6.84; Cl 17.21. $C_{21}H_{28}Cl_2O_4$. Calculated, %: C 60.73; H 6.79; Cl 17.07.

4-Hydroxy-4-[(*Z*)-oct-2-enyl]-2,3-dichlorocyclopent-2-en-1-one (IV). To a solution of 0.5 g (1.8 mmol) of diol **XII** in 50 ml of acetone at 0°C was added dropwise 1.8 ml of Jones' reagent prepared from 0.34 g of CrO_3, 1.5 ml of H_2O, and 0.3 ml of H_2SO_4. The reaction mixture was stirred for 30 min, the excess Jones' reagent was destroyed with 0,3 ml of 2-propanol, and 20 ml of saturated aqueous NaCl solution was added thereto. The reaction products were extracted into ethyl ether (3×50 ml), the combined extracts were washed with 10 ml of saturated aqueous NaCl solution, dried with $MgSO_4$, evaporated, and the residue was subjected to chromatography on silica gel to afford 0.34 g (74%) of oily compound **IV**. IR spectrum (ν, cm^{-1}): 1614, 1740, 3480. ^1H NMR spectrum (δ, ppm): 0.89 t (3H, CH_3, *J* 7 Hz), 1.10–1.40 m (6H, $3CH_2$), 1.90–2.65 m (4H, $2CH_2$), 2.70 d (1H, C^5H, *J* 18.3 Hz), 2.86 d (1H, C^5H, *J* 18.3 Hz), 2.60–2.90 m (1H, OH), 5.10–5.25 m (1H, CH=), 5.60–5.72 m (1H, CH=). ^{13}C NMR spectrum (δ_C, ppm): 13.99 (CH_3), 22.48 ($C^{7'}$), 26.43 ($C^{4'}$), 27.53 ($C^{6'}$), 31.46 ($C^{5'}$), 36.39 ($C^{1'}$), 47.26 (C^5), 77.44 (C^4), 120.31 ($C^{2'}$), 131.37 (C^2), 136.65 ($C^{3'}$), 164.73 (C^3), 193.30 (C=O).

8-Allyl-8-hydroxy-1,4-dioxa-6,7-dichloro-spiro-[4.4]non-6-ene (V). To a vigorously stirred solution of 1 g (5.2 mmol) of ketone **I** and 0.83 g of allyl bromide in 15 ml of DMF was added 1 g (15.3 g-at) of zinc. The reaction started with heat evolution that ended in 30 min. The reaction mixture was acidified with a saturated solution of NH_4Cl, the reaction product was extracted into ether (3 × 30 ml), the extract was dried on $MgSO_4$, evaporated, and the residue was subjected to chromatography on SiO_2. We obtained 1.15 g (85%) of oily alcohol **V**. IR spectrum (ν, cm^{-1}): 1615, 3100, 3450. ^1H NMR spectrum (δ, ppm): 2.17 d (1H, 0.5 CH_2, *J* 14.2 Hz), 2.32 d.d (1H, CH_2, *J* 13.7, 7.3 Hz), 2.46 d (1H, C^9H, *J* 14.2, 7.3 Hz), 2.48 d (1H, CH_2, *J* 13.7 Hz), 3.32 br.s (1H, OH), 3.85–4.20 m (4H, $2CH_2O$), 5.05–5.17 five m (2H, CH_2=), 5.60–5.75 m (1H, CH=). ^{13}C NMR spectrum (δ_C, ppm): 42.36 (CH_2), 47.82 (C^9), 65.92 (C^2, C^3), 78.69 (C^8), 112.22 (C^5), 119.62 (CH_2=), 131.82 (CH=), 132.18 (C^7), 139.58 (C^6).

8-Allyl-4-hydroxy-2,3-dichlorocyclopent-2-en-1-one (VI). A solution of 0.65 g (2 mmol) of ketal **V** in 10 ml of acetone and 0.2 ml of 15% aqueous HCl was refluxed for 1 h, the reaction mixture was cooled to 20°C, and 2 ml of saturated aqueous NaCl solution was added thereto. The reaction product was extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were washed with the saturated aqueous NaCl solution till neutral, dried on $MgSO_4$, filtered, and evaporated to obtain 0.46 g (82%) of ketone **VI**. IR spectrum (ν, cm^{-1}): 850, 1615, 1680, 1740, 3100, 3450. ^1H NMR spectrum (δ, ppm): (1H, CH_2, *J* 13.6, 7.1 Hz), 2.52 d.d (1H, CH_2, *J* 13.6, 7.1 Hz), 2.58 d (1H, C^5H, *J* 18.5 Hz), 2.80 d (1H, C^5H, *J* 18.5 Hz), 4.30 br.s (1H, OH), 5.05–5.17 m (2H, CH_2=), 5.60–5.75 m (1H, CH=). ^{13}C NMR spectrum (δ_C, ppm): 42.09 (CH_2), 46.80 (C^5), 77.04 (C^4), 120.97 (CH_2=), 130.22 (CH=), 132.73 (C^2), 165.83 (C^3), 194.43 (C=O).

4-Allyl-4-methoxymethoxy-2,3-dichlorocyclopent-2-en-1-one (VII). To a stirred solution of 0.43 g (1.54 mmol) of alcohol **VI** and 0.24 g (3 mmol) of chloromethyl ether in 10 ml of anhydrous dichloro-

ethane 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 MgO_4, filtered, and evaporated. We obtained 0.46 g (92%) of compound **VII**. IR spectrum (ν, cm^{-1}): 850, 1630, 1670, 1760, 3110. ^{1}H NMR spectrum (δ, ppm): 2.43 d.d (1H, CH_2, *J* 13.7, 7.3 Hz), 2.63 d.d (1H, CH_2, *J* 13.7, 7.3 Hz), 2.68 d (1H, C^5H, *J* 18.8 Hz), 2.97 d (1H, C^5H, *J* 18.8 Hz), 3.28 s (3H, OMe), 4.55 s (2H, OCH_2O), 5.05–5.15 m (2H, CH_2=), 5.45–5.60 m (1H, CH=). ^{13}C NMR spectrum (δ_C, ppm): 41.74 (CH_2), 43.37 (C^5), 55.75 (OMe), 81.92 (C^4), 91.12 (OCH_2O), 120.83 (CH_2=), 130.17 (CH=), 135.13 (C^2), 162.49 (C^3), 192.74 (C=O).

4-Allyl-4-methoxymethoxy-2,3-dichlorocyclopent-2-en-1-ol (VIII). To a solution of 2 g (9.7 mmol) of ketone **VII** in 50 ml of EtOH was added at 0°C a freshly prepared solution of 1.2 g (31.8 mmol) of $NaBH_4$ in 25 ml of EtOH. The mixture was stirred for 30 min, then 15 ml of MeOH was added, the mixture was acidified with 3% aqueous HCl till pH 5, and the reaction products were extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with water solution of NaCl (2 × 30 ml), dried with $MgSO_4$, the solution was evaporated at reduced pressure to obtain 3.72 g (91%) of alcohol (**VIII**) (diastereoisomers mixture, 2:1). IR spectrum (ν, cm^{-1}): 1670, 3110, 3450. ^{1}H NMR spectrum (δ, ppm): 1.80–2.60 m (4H, $2CH_2$), 3.24 s and 3.32 s (3H, OMe), 4.20–4.75 m (4H, OCH_2O, OH, C^4H), 5.00–5.10 m (2H, CH_2=), 5.45–5.70 m (1H, CH=). ^{13}C NMR spectrum(δ_C, ppm): 40.34 and 40.83 (CH_2), 42.36 and 42.60 (C^5), 55.16 and 55.33 (OMe), 72.90 and 72.96 (C^4), 85.52 and 86.24 (C^4), 91.50 (OCH_2O), 119.12 and 119.44 (CH_2=), 131.22 and 131.83 (CH=), 132.84 and 133.10 (C^3), 137.00 and 137.14 (C^2).

1-Allyl-4-(*tert*-butyldimethylsilyloxy)-1-methoxymethoxy-2,3-dichlorocyclopent-2-ene (IX). To a solution of 2 g (11.62 mmol) of alcohol **VIII** and 1.26 g (17.42 mmol) of imidazole in 20 ml of DMF was added dropwise under argon at –10°C within 10 min a solution of 1.93 g (12.78 mmol) of *tert*-butyldimethylsilyl chloride in 10 ml of DMF. The reaction mixture was stirred at 0°C for 1 h, then 100 ml of water was added, and the products were extracted with ether (3ξ50 ml). The ether extracts were 3 times washed with saturated aqueous NaCl solution. dried with anhydrous $MgSO_4$, evaporated, and the oily residue was subjected to chromatography on Si)$_2$ (eluent hexane–ethyl acetate, 7:2). We obtained 2.48 g (84%) of compound **IX**. IR spectrum (ν, cm^{-1}): 1650, 3100. ^{1}H NMR spectrum (δ, ppm): 0.11 s and 0.13 s (6H, 2Me), 0.91 s (9H, 3Me), 2.00– 2.70 m (4H, $2CH_2$), 3.38 s (3H, CH_3O), 4.40–5.00 m (3H, CH_2, OH), 5.10–5.30 m (2H, CH_2=), 5.50–5.90 m (1H, CH=). ^{13}C NMR spectrum (δ_C, ppm): –3.95 (2Me), 18.21 (SiC), 25.27 (3Me), 41.46 and 42.47 (CH_2), 42.80 and 43.21 (C^5), 55.77 (OMe), 73.35 and 74.36 (C^4), 85.66 and 86.81 (C^1), 91.92 and 92.05 (OCH_2O), 119.12 and 119.57 (CH_2=), 131.98 and 132.47 (CH=), 132.97 and 134.42 (C^3), 135.65 and 137.45 (C^2).

4-(*tert*-Butyldimethylsilyloxy)-1-methoxymethoxy-1-[(Z)-oct-2-enyl]-2,3-dichlorocyclopent-2-ene (XI). To a solution of 2 g (5.64 mmol) of olefin **IX** in 50 mg of THF was added 10 mg of OsO_4, the mixture was stirred for 15 min, and then a solution of 5.5 g (25.7 mmol) of $NaIO_4$ in 35 ml of water was added. On completion of the reaction (TLC monitoring) the reaction mixture was filtered, the precipitate was washed with 20 ml of ethyl acetate, and the reaction products were extracted with ethyl acetate (3×40 ml) from the filtrate. The combined organic solutions were washed with a saturated aqueous NaCl solution, dried with $MgSO_4$, filtered, and evaporated to obtain 1.84 g (92%) of aldehyde **X**. IR spectrum (ν, cm^{-1}): 800, 1650, 1730, 2770. Aldehyde **X** was dissolved in 20 ml of benzene and was added dropwise to a solution of ylide prepared by treating a suspension of 3.42 g (8 mmol) of hexyltriphenylphosphonium bromide in 20 ml of benzene with 14.55 ml 0.55 N benzene solution of $(Me_3Si)_2NNa$ (Ar, 30 min). The mixture was stirred for 3 h, then acidified with 0.5 N water solution of HCl till pH 7, and the reaction products were extracted into ethyl ether (4ξ10 ml). The combined organic extracts were washed with saturated water solution of NaCl, dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was subjected to chromatography on SiO_2 (eluent ethyl acetate–hexane, 3:7, R_f 0.32) to furnish 0.77 g (78%0 of oily substance **XI**. IR spectrum (ν, cm^{-1}): 1545, 3030. ^{1}H NMR spectrum (δ, ppm): 0.02 s (3H, SiMe), 0.04 s (3H, SiMe), 0.81 t (3H, CH_3, *J* 7 Hz), 0.83 s (9H, CMe_3), 1.15–1.40 m (6H, $3CH_2$), 1.70–2.60 m (6H, $3CH_2$), 3.29 s and 3.30 s (3H, OMe), 5.00–5.10 m and 5.40–5.50 m (2H, CH=CH). ^{13}C NMR spectrum (δ_C, ppm): –4.68 (SiMe), –4.83 (SiMe), 13.98 (CH_3), 18.05 (SiC), 22.44 and 22.50 ($C^{7'}$), 25.60 (3Me), 27.46 ($C^{4'}$), 29.02 and 29.19 ($C^{6'}$), 31.19 and 31.47 ($C^{5'}$), 35.79 and 36.22 ($C^{1'}$), 41.42 and 41.55 (C^5), 55.60 (OMe), 73.30 and 74.23 (C^4), 86.01 and 87.03 (C^1), 91.78 and 91.90 (OCH_2O), 122.06 and 122.58

($C^{3'}$), 134.19 and 134.42 ($C^{2'}$), 133.58 (C^{3}), 135.35 and 135.93 (C^{2}).

4-Hydroxy-4[(*Z*)-oct-2-enyl]-2,3-dichlorocyclopent-2-en-1-ol (XII). A mixture of 1.42 g (7.3 mmol) of compound **X** and 1.72 g (7.35 mmol) of tetrabutylammonium fluoride in 7.5 ml of THF was stirred at room temperature for 2 h. Then the reaction mixture was diluted with 200 ml of ether, washed in succession with 40 ml of $NaHCO_3$ water solution and 80 ml of saturated water solution of NaCl, and dried on $MgSO_4$. The solution was evaporated, and the residue was subjected to chromatography on SiO_2 (eluent hexane–ethyl acetate, 4:1, R_f 0.11) to obtain 1.41 g of oily substance that was dissolved in 10 ml of a mixture acetone–0.2 ml of 15% HCl solution. The reaction mixture was maintained at 20°C for 2 h, then 2 ml of saturated aqueous NaCl solution was added, the hydrolysis product was extracted into ethyl acetate (3×10 ml). The combined organic extracts were washed with saturated aqueous NaCl solution till neutral, dried with $MgSO_4$, filtered, and evaporated to obtain 0.27 g (64%) of diol **XII**. IR spectrum (ν, cm^{-1}): 1545, 3030, 3400. ^1H NMR spectrum (δ, ppm): 0.87 t (3H, CH_3, *J* 7 Hz), 1.20–1.50 m (6H, $3CH_2$), 1.70–2.70 m (6H, $3CH_2$), 3.20–3.50 m (1H, OH), 4.10–4.70 m (2H, OH, C^4H), 5.00–5.70 m (2H, CH=CH). ^{13}C NMR spectrum (δ_C, ppm): 13.91 (CH_3), 22.40 ($C^{7'}$), 27.39 ($C^{4'}$), 29.07 ($C^{6'}$), 31. 36 ($C^{5'}$), 35.69 and 36.51 ($C^{1'}$), 44.18 and 44.42 (C^{5}), 72.93 and 73.41 (C^{4}), 80.77 and 80.98 (C^{1}), 121.54 and 122.34 ($C^{2'}$), 133.41 and 134.27 (C^{3}), 134.72 and 135.00 ($C^{3'}$), 136.15 and 136.84 (C^{2}).

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