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Prostanoids: LXXIV.* 2,3-Dichloro-4,4-ethylenedioxy-2-cyclopentenone in the Synthesis of Analogs of Marine Prostanoids**

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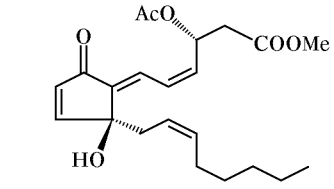
Abstract—Transformations of readily accessible 2,3-dichloro-4,4-ethylenedioxy-2-cyclopentenone resulted in formation of previously unknown 2,3-dichloro-4-hydroxy-4-[(*Z*)-2-octenyl]-2-cyclopentenone which is a universal block synthon for analogs of marine prostanoids.

Prostanoids (PG) with unusual structure, such as clavulones [2, 3] (isolated from marine corals) and related halogen-containing compounds, chlorovulones [4], punaglandins [5, 6], etc. [7], attract considerable interest due to their powerful antiviral and antineoplastic activity [8]. The structures of some most important marine prostanoids are shown in Scheme 1.

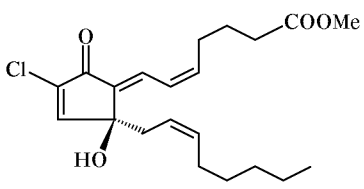
The structural fragment in marine prostanoid molecules responsible for their antiviral and antitumor activity is the cross-conjugated dienone system which includes the C^9=O keto group and C^7=C^8 and C^{10}=C^{11} double bond. The presence of a hydroxy group at C^{12}, as well as of chlorine atom on C^{10}, enhances the biological activity. The antitumor effect of chlorinated prostanoids is stronger than that of clavulones; in turn, punaglandins are more active than chlorovulones [10].

It is known that among native PGs possessing antitumor activity the most efficient are alkylidenecyclopentene derivatives like PGA_1 and J_2. Methyl esters Δ^7-PGA_1 and Δ^{12}-PGJ_2 (Scheme 1) are characterized by IC_{50} values of 0.3 and 0.7 μg/ml, respectively,

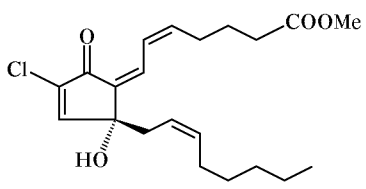
Scheme 1.



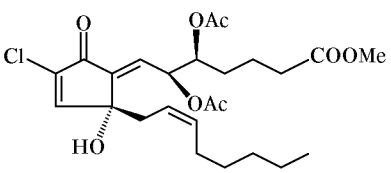
Clavulone I



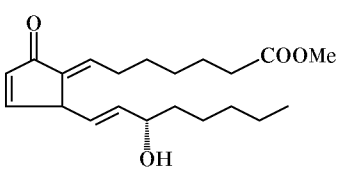
Chlorovulone I



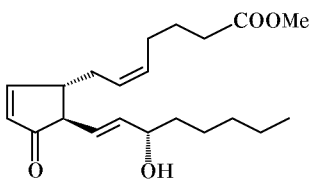
Chlorovulone IV



Punaglandin IV



Δ^7-PGA_1



Δ^{12}-PGJ_2

* For communication LXXIII, see [1].

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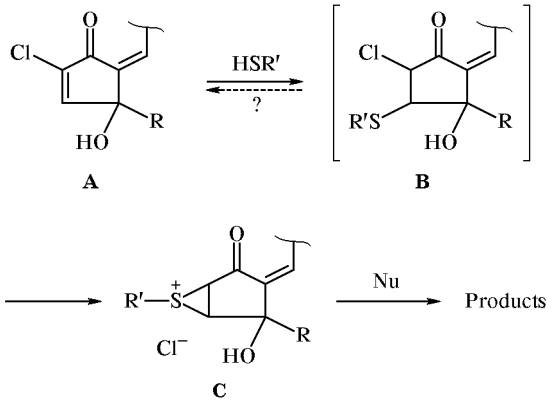
against L1210 cells *in vitro*; the corresponding IC_{50} value for clavulones is 0.5 μg/ml, and for punaglandins, 0.02 μg/ml; i.e., these are lower than those found for the known antitumor agents, Vincristine and Doxorubicin. The antiproliferative activity increases in the series: methyl esters PGA_1 and PGJ_2 < Δ^{12}-PGJ_2 < methyl ester Δ^7-PGA_1 ≈ clavulones < chlorovulones < punaglandins [9–11].

The mechanism of antitumor action of Δ^{12}-PGJ_2 and Δ^7-PGA_1 is unique [11]; it originates from their ability to penetrate cell membranes and irreversibly (in physiological medium) bind nucleic proteins via covalent bonds. The latter are formed by 1,4-addition of the protein thiol groups to the enone system of prostaglandins (at C^{11}). The result is that PGs inhibit biosynthesis of macromolecules (such as proteins and DNAs) and hence cell proliferation, i.e., the cell cycle is terminated at the G^1 phase. It is important that PGs bind only to the nucleic proteins: their reactions with HSR at the approach to cell nucleus and even in the intracellular space are reversible (direct PG–glutathione conjugates exhibit no antiproliferative activity, and they are not transferred to cell nucleus). This is the main distinctive feature of the antitumor action of alkylidene prostaglandins. It should be noted that methyl ester Δ^7-PGA_1, which is effective in the treatment of chemotherapy-resistant ovary cancer by intraperitoneal administration [12], is now under preclinical testing.

Unlike Δ^{12}-PGJ_2 and Δ^7-PGA_1, the mechanism of antitumor action of chlorine-containing marine PGs (chlorovulones and punaglandins) is not so clear and doubtless [8, 13]. It was reported that these compounds inhibit biosynthesis of proteins, DNAs, and cell proliferation as a whole, but no chemical aspects of such action were considered [13]. The molecular structure of chlorovulones and punaglandins suggests that these, as well as Δ^{12}-PGJ_2 and Δ^7-PGA_1, are alkylating agents. The presence of C^{10}–Cl and C^{12}–OH moieties provides additional activation of the enone system as Michael acceptor. However, in this case the unique mechanism typical of Δ^{12}-PGJ_2 and Δ^7-PGA_1 (involving irreversible reaction with thiol groups of only nucleic proteins) may not be operative since primary conjugates **B** formed by chlorovulone and punaglandin analogs **A** can readily be transformed into other products through reactive episulfonium salts **C** (the reaction is irreversible; Scheme 2).

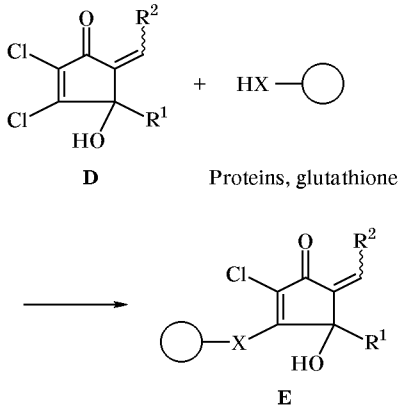
Scheme 2.



As noted above, the antitumor activity of chlorovulones and punaglandins (**A**) is even slightly higher than that of Δ^{12}-PGJ_2 and Δ^7-PGA_1. Assuming that the mechanisms of antitumor action of **A** and Δ^7-PGA_1 are similar, the reaction **A** + HSR ⇄ **B** on the path of PG to cell nucleus should be reversible; taking into account that the transition **A** → **B** is substantiated to a sufficient extent, we can presume usual alkylating mechainsm of the antitumor action of **A** (irreversible binding to thiol groups).

In the present work we made an attempt to synthesize new analogs of marine prostanoids of the general formula **D** which contain two chlorine atoms in positions *10* and *11* (PG numbering). Undoubtedly, these chlorine atoms should strongly enhance properties of the α,β-unsaturated cyclopentenone system as Michael acceptors, so that they should readily and irreversibly react with amino or thiol groups of proteins by the Ad_NE mechanism to give conjugates **E** (Scheme 3). Similar products **E** formed by reactions of simpler compounds, e.g., of 2,3-dichlorocyclopentenones with O-, S-, and especially N-nucleophiles, are extremely chemically stable [14, 15].

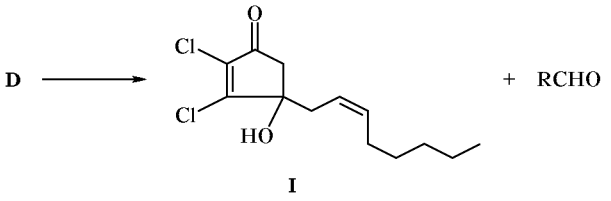
Scheme 3.



Thus, had compounds **D** exhibited antitumor activity, the mechanism of their action would be different

from that discussed above for Δ^7-PGA_1 because the reaction **D** → **E** is irreversible. Probably, compounds **D** should be powerful alkylating agents. Obviously, the results of our study will favor better understanding of mechanistic aspects of antitumor activity of halogen-containing marine prostanoids. It was supposed to obtain structures **D** by aldol-like condensation of aldehydes with enolate generated from enone **I** (Scheme 4).

Scheme 4.



I

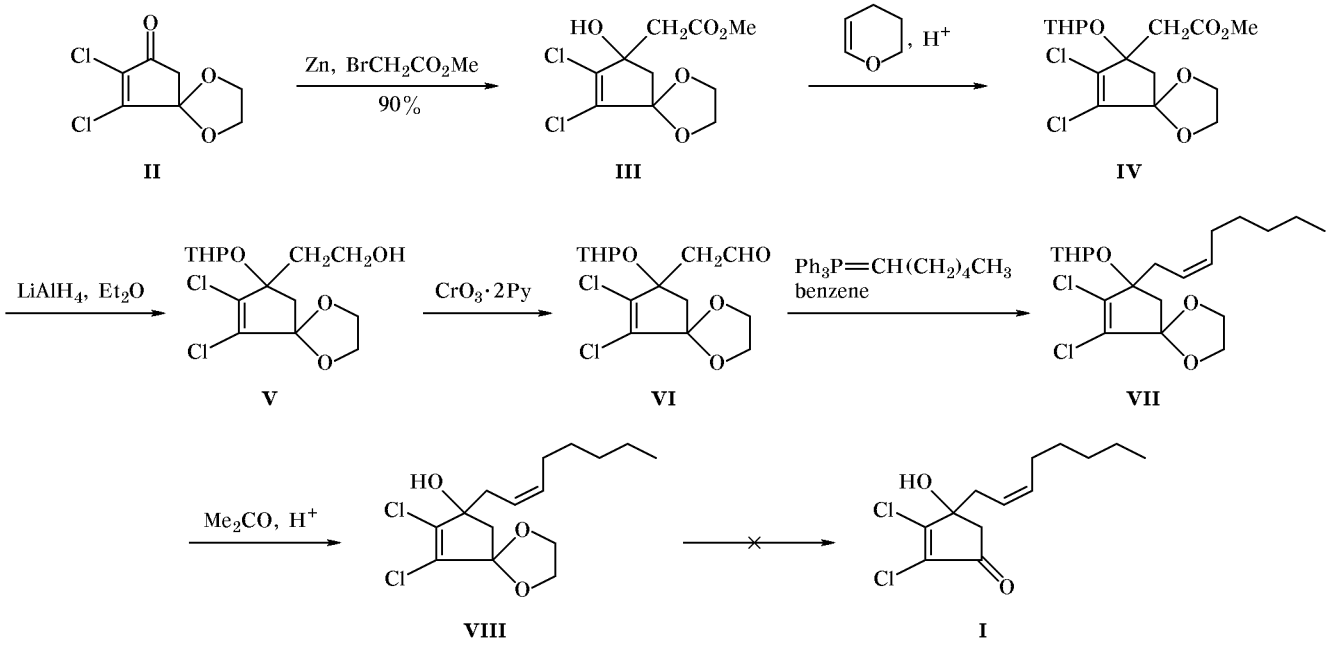
The synthetic approach to key compound **I** starts from readily accessible dichlorocyclopentenone **II** [16] (Scheme 5). We planned to build up the side chain through Reformatsky adduct **III** [1] and the subsequent transformation sequence **III** → **VII**. Acid hydrolysis of the tetrahydropyran-2-yloxy group in **VII** smoothly yielded the corresponding alcohol. However, we failed to remove the dioxolane protection from **VIII** despite numerous attempts and application of various procedures. Presumably, the high hydrolytic stability of the dioxolane ring in **VIII** results from the presence of the *Z*-double bond in the side chain, which sterically shields the dioxolane fragment.

Therefore, the synthetic scheme was changed so that to accomplish deprotection of the oxo group at an earlier stage (before formation of the *Z*-double bond; Scheme 6). The reaction sequence started from hydroxy ester **III** which was synthesized as shown in Scheme 5. Unlike compound **VII**, acid hydrolysis of **III** occurred extremely readily, and enone **IX** was obtained in high yield. Intramolecular assistance by a free hydroxy group was observed by us previously [18, 19]. Before building up the side chain, the keto group in enone **IX** was reduced to hydroxy (which may subsequently be oxidized). The reduction was performed using sodium tetrahydridoborate. The hydroxy groups in diastereoisomeric diols **X** thus obtained were protected via etherification with dihydropyran. The ester group in **XI** was reduced with lithium aluminum hydride to obtain alcohol **XII** which was oxidized to aldehyde **XIII** by treatment with Collins' reagent. Olefination of **XIII** with hexylidenetriphenylphosphorane gave compound **XIV**, and the latter was oxidized with Jones' reagent to obtain the target cyclopentenone **I** in moderate yield.

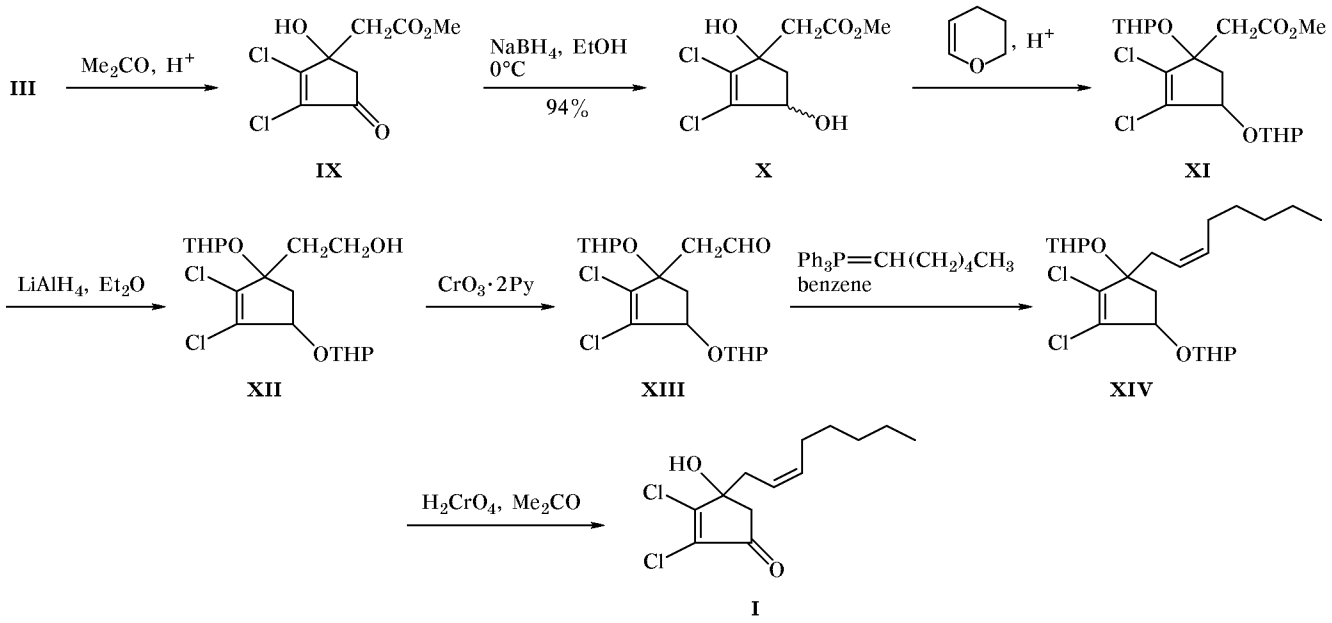
EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as thin films or mulls in Nujol. The ^1H and ^{13}C NMR spectra were obtained

Scheme 5.



Scheme 6.



on a Bruker AM-300 instrument at 300 MHz (^{1}H) and 75.47 MHz (^{13}C) using $CDCl_3$ as solvent and TMS as internal reference.

2,3-Dichloro-4-hydroxy-4-[(*Z*)-2-octenyl]-2-cyclopentenone (I). To a solution of 0.5 g (0.68 mmol) of bisether **XIV** in 50 ml of acetone at 0°C we added dropwise 2.9 ml of Jones' reagent prepared from 0.55 g of CrO_3, 5 ml of water, and 0.5 ml of concd. H_2SO_4. The mixture was stirred for 30 min, excess Jones' reagent was decomposed by adding 0.5 ml of 2-propanol, 20 ml of a solution of NaCl was added, and the product was extracted into ether (3 × 50 ml). The combined extracts were washed with 10 ml of a solution of NaCl, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography on silica gel to obtain 0.094 g (32%) of compound **I** as an oily substance. IR spectrum, ν, cm^{-1}: 1614, 1740, 3480. ^{1}H 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, 5-H, J = 18.3 Hz), 2.86 d (1H, 5-H, J = 18.3 Hz), 2.60–2.90 m (1H, OH), 5.10–5.25 m (1N, 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).

1,2-Dichloro-3-(2-tetrahydropyranyloxy)-3-(2-hydroxyethyl)-5,5-ethylenedioxycyclopentene (V). To a solution of 3 g (10.6 mmol) of alcohol **III** and 0.01 g of *p*-toluenesulfonic acid in 20 ml of CH_2Cl_2 at 0°C we added with stirring 1.16 g (13.8 mmol) of freshly distilled 2,3-dihydropyran. The mixture was stirred for 30 min, 0.1 g of $NaHCO_3$ was added, the solution was evaporated, and the residue was subjected to chromatography on silica gel to obtain 3.54 g (91%) of compound **IV**. The product was dissolved in 30 ml of ether, and 0.7 g $LiAlH_4$ was added. The mixture was stirred for 30 min, and 40 ml of moist ether and 7 ml of 10% aqueous potassium hydroxide were added. The organic layer was separated, dried over $MgSO_4$, and evaporated to obtain 2.68 g (82%) of diastereoisomeric alcohols **V** at a ratio of 4:1 (according to ^{1}H NMR). IR spectrum, ν, cm^{-1}: 3500. ^{1}H NMR spectrum, δ, ppm: 1.40–1.80 m (8H, $4CH_2$), 2.30–2.60 m (2H, C^9H_2), 2.82 br.s (1H, OH), 3.40–4.25 m (8H, $3CH_2O$), 4.55 m and 4.95 m (1H, 2″-H). ^{13}C NMR spectrum, δ_C, ppm: 19.45 and 20.20 ($C^{4''}$), 25.02 and 25.10 ($C^{5''}$), 31.45 and 31.64 ($C^{3''}$), 40.76 and 40.27 ($C^{1'}$), 46.31 and 46.25 (C^9), 58.83 ($C^{2'}$), 62.38 and 62.74 ($C^{6''}$), 65.98, 66.24, and 66.33 (CH_2O), 85.33 and 84.26 (C^8), 93.54 and 95.01 ($C^{2''}$), 112.31 (C^5), 134.49 (C^7), 137.55 (C^6).

1,2-Dichloro-3-(2-tetrahydropyranyloxy)-3-[(*Z*)-2-octenyl]-5,5-ethylenedioxycyclopentene (VII). A solution of 1.32 g (3.9 mmol) of alcohol **V** in 10 ml of CH_2Cl_2 was added at 0°C with vigorous stirring under argon to Collins' reagent prepared from 5.6 g (56.0 mmol) of CrO_3 and 9.58 ml of pyridine in 70 ml of CH_2Cl_2. After 15 min (TLC), the mixture was filtered through a thin layer of silica gel, the filtrate was acidified to pH 6 with 2 N hydrochloric acid, and the organic phase was separated, washed with

a saturated aqueous solution of NaCl (3 × 30 ml), dried over $MgSO_4$, and evaporated under reduced pressure. We thus isolated 1.1 g (84%) of aldehyde **VI**. IR spectrum, ν, cm^{-1}: 1632, 1672, 1724, 1744. Aldehyde **VI**, 1.1 g, was dissolved in 25 ml of benzene, and the solution was added to a solution of hexylidenetriphenylphosphorane, prepared by treatment of a suspension of 4.46 g (105.1 mmol) of hexyltriphenylphosphonium bromide in 10 ml of benzene with 10 ml of a 0.55 N benzene solution of $(Me_3Si)_2NNa$ (30 min, argon atmosphere). The mixture was stirred for 3 h, neutralized to pH 7 with 0.5 N hydrochloric acid, and extracted with diethyl ether (4 × 10 ml). The combined extracts were washed with a saturated aqueous solution of NaCl (5 ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel (eluent ethyl acetate–hexane, 3:7; R_f 0.32). Yield of **VII** 0.77 g (58%; diastereoisomeric mixture), oily substance. IR spectrum, ν, cm^{-1}: 1600. ^1H NMR spectrum, δ, ppm: 0.83 t (3H, CH_3, J = 7 Hz), 1.10–1.70 m (12H, $6CH_2$), 1.70–2.60 m (6H, $3CH_2$), 3.80–4.10 m (6H, $3CH_2O$), 4.50 m and 4.85 m (1H, 2″-H), 5.20–5.35 m (1H, CH=), 5.40–5.55 m (1H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 13.90 (CH_3), 19.47 and 20.85 ($C^{4''}$), 22.41 ($C^{7'}$), 25.06 ($C^{5''}$), 27.32 ($C^{4'}$), 27.58 ($C^{6'}$), 31.37 ($C^{3''}$), 31.40 ($C^{5'}$), 31.69 ($C^{1'}$), 43.24 and 45.09 (C^9), 63.14 ($C^{6''}$), 65.83, 66.06, 66.87, and 66.96 (CH_2O), 84.80 (C^8), 94.53 and 94.68 ($C^{2''}$), 112.31 (C^5), 122.33 ($C^{2'}$), 133.71 ($C^{3'}$), 134.23 (C^7), 137.64 (C^6).

(±)-1,2-Dichloro-3-hydroxy-3-[(*Z*)-2-octenyl]-5,5-ethylenedioxycyclopentene (VIII). To a solution of 0.77 g (1.89 mmol) of compound **VII** in 10 ml of acetone we added 0.2 ml of 15% hydrochloric acid and, 2 h after, 2 ml of a saturated aqueous solution of NaCl. The product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were washed with a saturated aqueous solution of NaCl until neutral reaction, dried over $MgSO_4$, filtered, and evaporated to obtain 0.51 g (82%) of alcohol **VIII**. IR spectrum, ν, cm^{-1}: 1636, 3440. ^1H NMR spectrum, δ, ppm: 0.79 t (3H, CH_3, J = 7 Hz), 1.10–1.40 m (6H, $3CH_2$), 1.85–2.60 m (6H, $3CH_2$), 2.70–3.00 (1H, OH), 3.80–4.10 m (4H, $2CH_2O$), 5.15–5.30 m (1H, CH=), 5.40–5.60 m (1H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 14.12 (CH_3), 22.85 ($C^{7'}$), 27.73 ($C^{4'}$), 29.72 ($C^{6'}$), 31.82 ($C^{5'}$), 36.20 ($C^{1'}$), 43.29 (C^9), 66.35 and 66.46 (2C, CH_2O), 79.52 (C^8), 112.59 (C^5), 123.13 ($C^{2'}$), 132.43 (C^7), 134.86 ($C^{3'}$), 140.15 (C^6).

Methyl 2,3-dichloro-1,4-dihydroxy-2-cyclopentenylacetate (X). To a solution of 5 g (17.66 mmol) of ester **III** in 40 ml of acetone we added with stirring 1 ml of 15% hydrochloric acid and, 15 min after, 15 ml of a saturated aqueous solution of NaCl. The product was extracted into ethyl acetate (3 × 50 ml). The combined extracts were washed with a saturated aqueous solution of NaCl until neutral reaction, dried over $MgSO_4$, filtered, and evaporated to obtain 3.8 g (82%) of ketone **IX**. IR spectrum, ν, cm^{-1}: 1608, 1736, 3440. Ketone **IX** was dissolved in 50 ml of EtOH, the solution was cooled to 0°C, and a freshly prepared solution of 0.6 g (15.9 mmol) of $NaBH_4$ in 25 ml of EtOH was added. The mixture was stirred for 30 min, diluted with 15 ml of methanol, acidified to pH 5 with 3% hydrochloric acid, and extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with an aqueous solution of NaCl (2 × 30 ml), dried over $MgSO_4$, and evaporated under reduced pressure to obtain 3.72 g (91%) of diol **X** as a 4:1 mixture of diastereoisomers. IR spectrum, ν, cm^{-1}: 1650, 1740, 3450. ^1H NMR spectrum, δ, ppm: 1.90–2.95 m (4H, $2CH_2$), 3.64 s (3H, CH_3O), 4.00–4.30 m (1H, OH), 4.40–4.80 m (2H, 4-H, OH). ^{13}C NMR spectrum, δ_C, ppm: 41.72 and 42.29 (C^5), 45.11 and 45.41 (CH_2), 51.55 and 51.77 (OMe), 72.33 and 73.00 (C^4), 78.23 and 78.92 (C^1), 134.29 and 134.85 (C^2), 134.89 and 135.19 (C^3), 170.55 and 171.38 (CO_2).

Methyl 2,3-dichloro-1,4-bis(2-tetrahydropyranyloxy)-2-cyclopentenylacetate (XI). To a solution of 3.72 g (14.5 mmol) of alcohol **X** and 0.01 of *p*-toluenesulfonic acid in 20 ml of methylene chloride at 0°C we added with stirring 3.16 g (37.6 mmol) of freshly distilled 2,3-dihydropyran. The mixture was stirred for 30 min, 0.1 g of $NaHCO_3$ was added, and the solution was evaporated to obtain 5.66 g (92%) of compound **XI**. IR spectrum, ν, cm^{-1}: 1636, 1740. ^1H NMR spectrum, δ, ppm: 1.20–1.80 m (12H, $6CH_2$), 1.80–3.00 m (4H, $2CH_2$), 3.50 s, 3.52 s, and 3.54 s (3H, CH_3O), 3.20–4.00 (4H, $2CH_2O$), 4.30–4.70 m (3H, 2CHO, 4-H).

1,2-Dichloro-3-[(*Z*)-2-octenyl)-3,5-bis(2-tetrahydropyranyloxy)cyclopentene (XIV) was obtained from diether **XI**, following the procedure described above for compound **VII**. Yield 71% (calculated on **XI**), oily substance. IR spectrum, ν, cm^{-1}: 1600. ^1H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3, J = 7 Hz), 1.20–2.70 m (20H, $10CH_2$), 3.10–4.20 m (6H, $2CH_2O$, 1′-H, 5-H), 4.70–5.00 m (3H, 2CHO, 4-H), 5.30–5.50 m (1H, CH=), 5.50–5.70 m (1H, CH=).

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