New 9β-halogenated Prostaglandine Analogues with an Ester Group at C-6 of the α-side Chain

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δ-Lactone prostaglandin intermediates with ω-side chain built were opened with diols in acid catalysis (TsOH) reaction to 9β-halogeno-15-keto-prostaglandin compounds. As diols, HO(CH$_2$)nOH, with n = 2 to 6 and also 2-butyne-1,4-diol were used. These compounds have an ester group in the position 6 of prostaglandin α-side chain and an alcohol group instead of C-1 carboxyl group spaced by two to 6 methylene group from the oxygen of the ester group. The reduction of enone group of the new 9β-halogeno-prostaglandin analogues with diisobornyloxyaluminium isopropoxide at -70°C was not selective, and the allylic alcohols were obtained pure as oils. Even the reduction of the starting δ-lactone prostaglandin intermediates was not selective. The allylic δ-lactone intermediates were also opened with 1,4-butane-diol and the allylic alcohols had the same structure as those obtained by reduction of 9β-halogeno-15-keto-prostaglandin compounds. The new prostaglandin analogues were characterized by elemental analysis, optical rotation for optically active compounds, IR, ^{1}H- ^{13}C- and 2D-NMR.

Keywords: 9β-halogeno-15-keto-prostaglandin analogues; 9β-halogeno-15-hydroxy-prostaglandin analogues; δ-lactone halogeno-prostaglandin intermediates, X-ray-crystallography; diols; enone reduction; NMR-analysis

Until present, a number of halogenated prostaglandin analogues were synthesized. Mostly, the halogen: chlorine, fluorine or bromine, was introduced at 9 (9α or 9β) or 11 (11α or 11β) position of the prostaglandins and their biological activity is determined as for the majority of prostaglandin analogues, especially by the structure of ω-side chain. For example, *Nocloprost* exhibits cytoprotective (anti-ulcer) activity, ZK-118182 and flunoprost have antitrombotic activity, 13,14-dihydro-ZK-118182(AL-6556) (fig 1) reduces intraocular pressure, etc.

It is considered that 9-halogenated prostaglandins can mimic the 9-keto group and acts at the receptors of PGE_2. The same is considered for 11-halogenated prostaglandins that have great affinity for receptors of PGD_2, like for example compound ZK 110841.

The synthesis of 9 or 11-halogenated prostaglandins was realized starting from the parent hydroxy-prostaglandin mainly by the sequence: mesylation or tosylation of the hydroxyl group and, the good leaving group so introduced, substituted in an SN2 reaction with the halogen atom of an organic quaternary ammonium reagent like tetra-butylamonium chloride or fluoride.

This sequence is exemplified by the following sequence (scheme 1) [1]:

The sequence was realized also for prostaglandin analogue ZK118182 [2]. Instead of a tetrabutylammonium

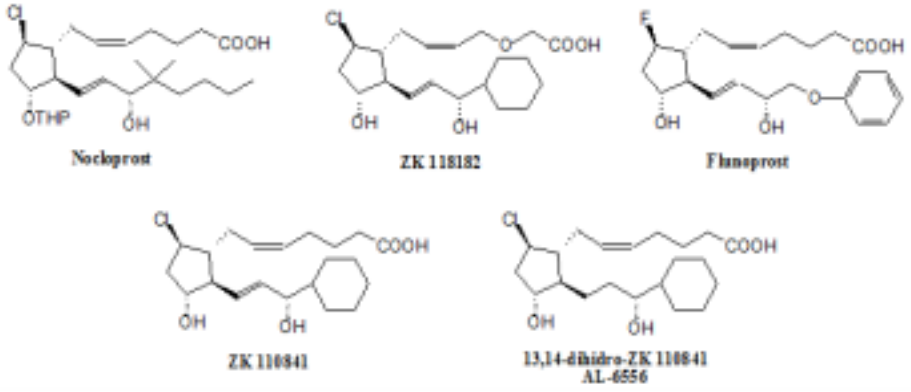
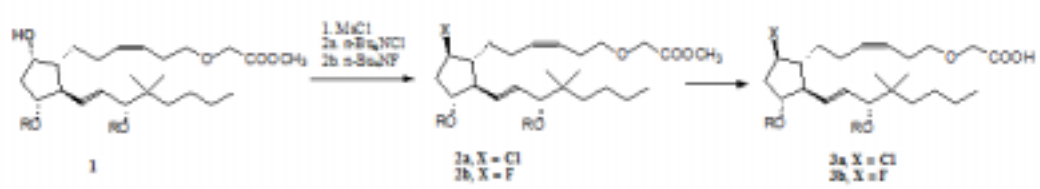


Fig. 1. Biological active 9-halogenated prostaglandin analogues



Scheme 1. Substitution of 9α-hydroxyl group on the prostaglandin $F_{2\alpha}$ analogue 1 with a 9β-halogen (chlorine and fluorine) in a sequence which include an intermediate mesylation

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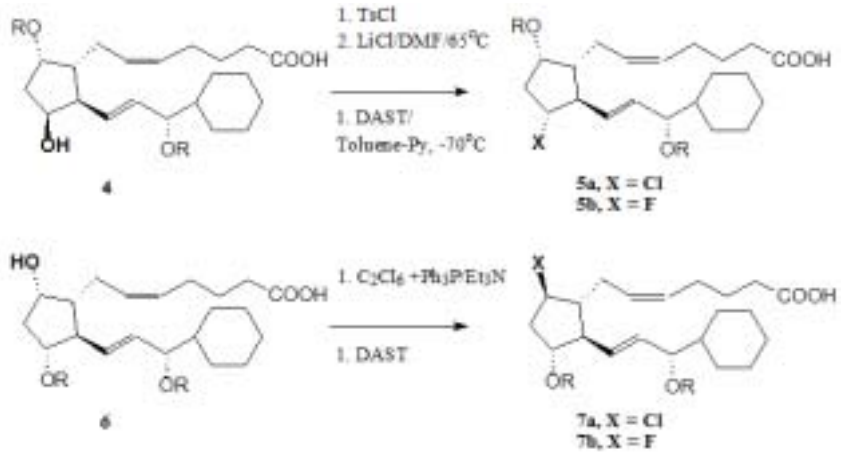


Scheme 2. Substitution of 11β and 9α-hydroxyl group on the prostaglandin $F_{2\alpha}$ analogues **4** or **6** with a 11α or 9β-halogen (chlorine and fluorine) atom.

halide, LiCl in DMF (65°C) was also used for a similar SN_2 substitution of a Ts group, **4→5a** scheme 2) [3]. OH group is also substituted by a chlorine atom with inversion of configuration by treatment with $C_2Cl_6/Ph_3P/Et_3N$ [3] (**6→7a**, or CCl_4/Ph_3P for 9 or 11-Cl-$PGF_{2\alpha}$ (scheme 2) [3,4].

For substitution of a hydroxyl group with a fluorine atom, some reagents were used: DAST or diethyl (2-chloro-1,1,2-trifluoroethyl)amine (scheme 2.), also with inversion of configuration.

The substitution of a hydroxyl group with a 9β-halogen (chlorine and fluorine) was realized also for a compound **8** from the intermediate stages of prostaglandin synthesis, with α-side chain already built (scheme 3) [5].

Only in a sequence for synthesis of Nocloprost the chlorine atom was kept from the starting intermediate **10** (scheme 4) [6]:

A 9β-bromine atom was introduced by reaction of 9α-hydroxy-16-phenoxy prostaglandin analogue with tetrabromomethane-triphenylphosphine-pyridine [7].

It is also to be mentioned that a serie of PGE_1 analogues with an ester group in the 6-position was synthesized by the reaction of an acid group with 2-chloro-1-methylpyridinium iodide and DMAP / $^iPr_2NEt$ in the first step, followed by reaction of the activated intermediate with alcohols [8]:

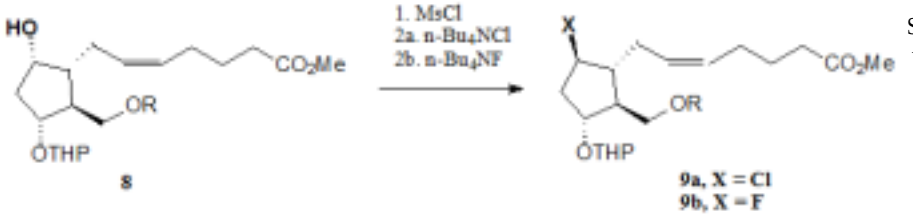
In this paper we realized the synthesis of 9β-halogen $PGF_{1\alpha}$ analogues with an ester group in the position 6, obtained from halogenated prostaglandin intermediates by reaction with two to six carbon atom diols.

Experimental part

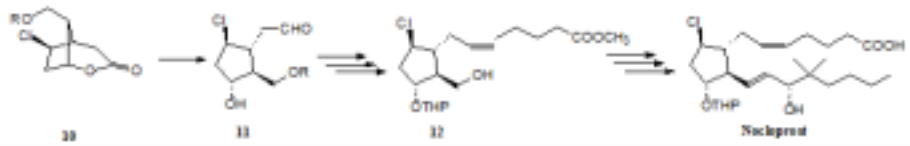
Melting points were determined on OptiMelt. The ^1H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^1H- NMR and at 75 MHz for ^{13}C-NMR, using $CDCl_3$ as solvent and TMS as internal standard. The numbering of the atoms is presented in the Schemes. The IR spectra (ATR) were recorded on a Vertex 70 Brucker instrument. TLC was performed on Merck silicagel 60 or $60F_{254}$ plates and spots were developed under UV light, with iodine and/or 15% H_2SO_4 in methanol and heating at 120-140°C.

General procedure for synthesis of prostaglandin analogues 17-21 from the intermediates 16

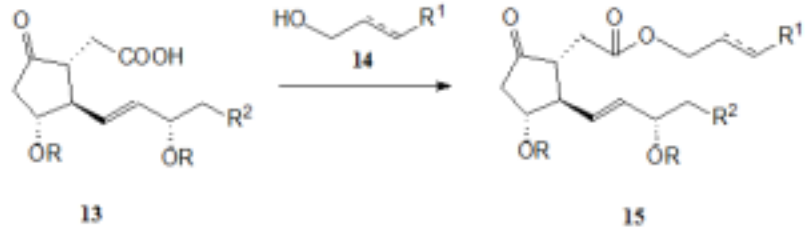
7.81 g (20 mM) (±)-exo-6-*halogeno*-3-exo-8-anti-4[-(3-*chloro or trifluoromethyl*-phenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]-octan and 4.18 g $TsOH·H_2O$ (22 mM) were dissolved in 40 mL anh. tetrahydrofurane (THF), the requested diol (mL) was added and the reaction mixture was stirred overnight at room temperature, monitoring the end of the reaction by TLC on silicagel plates, in the solvent system specified for each reaction. The reaction mixture was diluted with water (50 mL), THF was distilled under reduced pressure and the product multiple extracted with ether or ethyl acetate. The unified phases were washed with water, dried ($MgSO_4$), filtered off, concentrated and the crude product was purified by crystallyzation or by pressure chromatography (PC) on the solvent system specified for each reaction. The starting δ-lactone compound **16** is mentioned for each example.



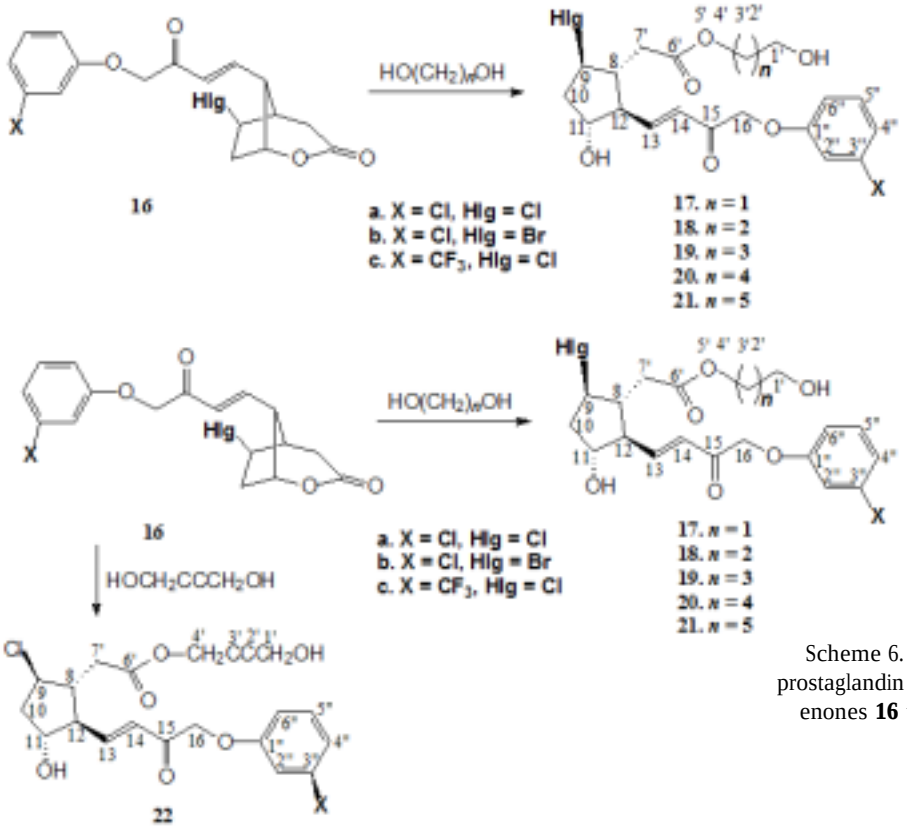
Scheme 3. Substitution of 9α-hydroxyl group with a 9β-halogen (Cl and F) in a sequence which include an intermediate mesylation on an intermediate **7** with the α-side chain already built



Scheme 4. Synthesis of Nocloprost from the starting chlorinated intermediate **10**



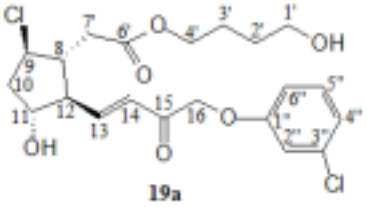
Scheme 5. Synthesis of PGE_1-6 esters **15** from the acid intermediate **13**



Scheme 6. Synthesis of 9β-halogenated prostaglandin analogues **17-21** by reaction of enones **16** with diols catalyzed by TsOH

When the quantities of the starting compound are different from that mentioned above, these are mentioned in each example and the other quantities of reagents and solvent are correspondingly calculated.

4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, 19a (X = Cl, Hlg = Cl).



19a

(±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]-octan; TLC (Silica gel, toluene-ethyl acetate, 1:1, $R_{f\ in}$ =0.62, $R_{f\ product}$ 0.27); the product was extracted with ether; 11 g of crude product resulted which was crystalyzed from ethanol-ethyl ether obtaining 5.9 g pure product, m.p. = 89-90°C (crystallized twice), elemental analysis, calculated for $C_{21}H_{26}Cl_2O_6$, th. (%), C: 56.63, Cl: 15.92, found (%): C: 56.30, Cl: 16.10,

IR (ATR): 3455s, 3369m, 3069w, 2956w, 2917w, 2898w, 1720vs, 1960s, 1620s, 1597s, 1583m, 1497m, 1445w, 1395w, 1361w, 1328m, 1301m, 1272w, 1223s, 1186m, 1154m, 1154m, 1081w, 1038s, 981m, 940m, 877w, 852w, 768m, 680w,

^{1}H-NMR-400MHz ($CDCl_3$, δ ppm, *J* Hz): 7.21 (t, 1H, H-5", 8.2), 6.96 (dd, 1H, H-4", 2.3, 8.2), 6.92 (dd, 1H, H-13, 8.6, 15.8), 6.90 (t, 1H, H-2", 2.3), 6.79 (dd, 1H, H-6", 2.3, 8.2), 6.45 (d, 1H, H-14, 15.8), 4.71 (s, 2H, H-16), 4.27 (q, 1H, H-11, 6.8), 4.18(q, 1H, H-9, 6.8), 4.07 (t, 2H, H-4', 6.4), 3.65 (t, 2H, H-1', 6.2), 2.57 (dd, 1H, H-7', 5.1, 14.8), 2.44(dt, 1H, H-7', 6.4, 14.8), 2.42-2.38 (m, 2H, H-8, H-12), 2.30 (t, 2H, H-10, 6.8), 2.09 (br s, 2H, OH), 1.70 (cv, 2H, H-3', 6.4), 1.60 (m cv, 2H, H-2', 6.0), ^{13}C-NMR-100MHz ($CDCl_3$, δ ppm): 194.58 (C-15), 171.40 (C-6'), 158.49 (1"), 148.04 (C-13), 135.11 (C-3"), 130.47 (C-5"), 126.86 (C-14), 122.07 (C-4"), 115.33 (C-2"), 113.13 (C-6"), 74.98 (C-11), 72.05 (C-16), 64.73 (C-4'), 62.23 (C-1'), 59.47 (C-9), 56.30 (C-12), 50.19 (C-8), 44.14 (C-10), 35.62 (C-7'), 29.08 (C-3'), 25.10 (C-2'),

By column chromatography purification on silica gel of the concentrated mother liquors (eluent: ethyl acetate-hexane, 1:1) 1.074 g pure product resulted, giving a total yield of 78.3%.

4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, 19b (X = Cl, Hlg = Br).

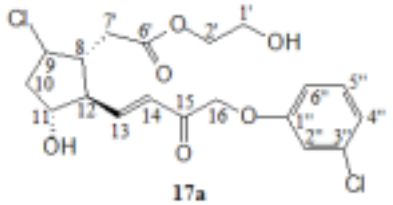
Starting from 5 mM (2.0 g) (±)-*exo*-6-bromo-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan, 2.98 g crude product were obtained. PC (benzene-ethyl acetate, 7:2); 1.3 g (53.8%) pure product **19b** were obtained, m.p. = 88-90°C (ethyl ether-heptane), containing at elemental analysis Cl+Br = 23.6% (th. 23.5%).

(-)-4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-3-hydroxy-2-((E)-3-oxo-4-(3-(trifluoromethyl) phenoxy)but-1-en-1-yl)cyclopentyl)acetate, 19c (X = CF_3, Hlg = Cl).

1 mM (389 mg) (-)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-trifluoromethyl-phenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]-octan; PC (eluent: ethyl acetate-hexane, 1:1); 357 mg (74.5%) of pure product **19c** as oil were obtained, $[\alpha]_D$ = -20.26 °(1% in THF), IR: 3406br m, 2941m, 1713s, 1623m, 1595w, 1493w, 1454m, 1326vs, 1289m, 1227m, 1165s, 1122vs, 1099m, 1063s, 978m, 875w, 790w, 697w, ^{1}H-NMR-300MHz ($CDCl_3$, δ ppm, *J* Hz): 7.41 (t, 1H, H-5", 8.2), 7.26 (m, 1H, H-4"), 7.15 (m, 1H, H-2"), 7.08 (dd, 1H, H-6", 2.3, 8.2), 6.95 (dd, 1H, H-13, 8.5, 15.7), 6.46 (d, 1H, H-14, 15.7), 4.79 (s, 2H, H-16), 4.28 (q, 1H, H-11, 6.9), 4.18 (q, 1H, H-9, 6.9), 4.07 (dt, 2H, H-4', 1.4, 6.3), 3.64 (dt, 2H, H-1', 1.4, 6.3), 2.57 (dd, 1H, H-7', 4.7, 14.7), 2.44 (dt, 1H, H-7', 6.6, 14.6), 2.42 (m, 2H, H-8, H-12), 2.31 (br t, 2H, H-10, 6.9), 1.68 (cv, 2H, H-3', 6.3), 1.60 (cv, 2H, H-2', 6.3), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 194.44 (C-15), 171.61 (C-

6'), 157.96 (1"), 148.38 (C-13), 132.13 (d, C-3", *J* = 32.6Hz), 130.37 (C-5"), 126.93 (C-14), 123.88 (q, CF_3, *J* = 272.5Hz), 118.66 (q, C-4", *J* = 3.5Hz), 118.17 (C-2"), 111.87 (q, *J* = 3.5Hz, C-6"), 74.98 (C-11), 71.99 (C-16), 64.84 (C-4'), 62.26 (C-1'), 59.58 (C-9), 56.38 (C-12), 50.21 (C-8), 44.18 (C-10), 35.73 (C-7'), 29.10 (C-3'), 25.14 (C-2').

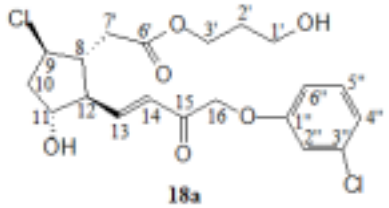
2-hydroxyethyl 2-((1R,2R,3R,5R)-5-chloro-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, 17a (X = Cl, Hlg = Cl).



17a

1.42 g (4 mM) (±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan, 0.76 g TsOH·H_2O, 10 mL ethylene glycol, 20 mLTHF; TLC (Silica gel, toluene-ethyl acetate, 1:1, $R_{f\ in}$ =0.62, $R_{f\ product}$ 0.25); 2.2 g crude product were purified by PC (eluent: ethyl acetate-heptane, 1:1), resulting a pure 0.7 g (41.9%) fraction of product **17a** as oil (the impure fraction of 0.85 g, containing >80%, was not purified), IR (nujol) : 3430-3380, 2940-2920, 2900-2890, 1730, 1700, 1625, 1600, 1480, 1440-1430, 1275, 1230, 870.

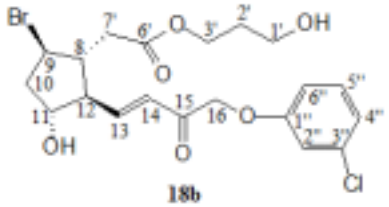
3-hydroxypropyl 2-((1R,2R,3R,5R)-5-chloro-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, 18a (X = Cl, Hlg = Cl).



18a

1.42 g (4 mM) (±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan, 20 mL 1,3-propanediol, 0.76 g TsOH·H_2O, 20 mL anh. THF; TLC (Silica gel, toluene-ethyl acetate, 1:1, $R_{f\ in}$ =0.62, $R_{f\ product}$ 0.28); a pure fraction of 0.85 g (49.3%) product **18a** was obtained as oil (another 0.72 g of >80% **18a** was obtained), elemental analysis calctd. for $C_{20}H_{24}Cl_2O_6$: th.(%): C: 55.69, H: 5.61, Cl:16,44; found (%): C: 55.41, H: 5.54, Cl: 16,58, IR (ATR): 3384br m, 2918s, 2850m, 1720vs, 1705m, 1691m, 1623s, 1595s, 1582m, 1477m, 1434w, 1402m, 1328m, 1299m, 1272w, 1223s, 1196m, 1158m, 1061m, 1029s, 980m, 945w, 891w, 758w, 677w, ^{1}H-NMR-300MHz ($CDCl_3$, δ ppm, *J* Hz): 7.23 (t, 1H, H-5", 8.2), 6.98 (dd, 1H, H-4", 1.9, 8.2), 6.90 (m, 1H, H-2"), 6.91 (dd, 1H, H-13, 7.1, 15.7), 6.79 (dd, 1H, H-6", 2.5, 8.2), 6.43 (d, 1H, H-14, 15.7), 4.73 (s, 2H, H-16), 4.26 (q, 1H, H-11, 6.8), 4.19 (q, 1H, H-9, 6.8), 4.04 (t, 2H, H-3', 6.6), 3.62 (t, 2H, H-1', 6.3), 2.48-2.36 (m, 4H, H-8, H-12, 2H-7'), 2.30 (br t, 2H, H-10, 6.8), 1.68-1.52 (m, 2H, H-2', 6.3), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 194.68 (C-15), 171.62 (C-6'), 158.48 (1"), 148.33 (C-13), 135.10 (C-3"), 130.56 (C-5"), 126.90 (C-14), 122.09 (C-4"), 115.30 (C-2"), 113.18 (C-6"), 74.92 (C-11), 71.94 (C-16), 64.91 (C-3'), 62.56 (C-1'), 59.57 (C-9), 56.34 (C-12), 50.15 (C-8), 44.13 (C-10), 35.67 (C-7'), 32.16 (C-2').

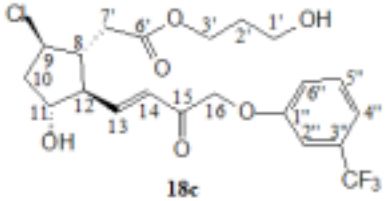
2-hydroxypropyl 2-((1R,2R,3R,5R)-5-bromo-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, 18b (X = Cl, Hlg = Br).



18b

2 g (5 mM) (±)-*exo*-6-bromo-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan; PC (eluent, benzene-ethyl acetate, 7:2); 1.213 g (51%) of pure product **18b** were obtained as oil, elemental analysis for Br: found 15.83% (th. 15.80%).

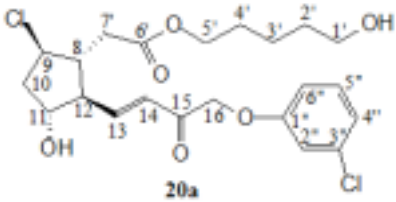
(-)-2-hydroxypropyl 2-((1R,2R,3R,5R)-5-chloro-3-hydroxy-2-((E)-3-oxo-4-(3-(trifluoromethyl) phenoxy)but-1-en-1-yl)cyclopentyl)acetate, (-)-18c (X = CF_3, Hlg = Cl).



18c

389 mg (1 mM) (-)-*exo*-6-chloro -3-*exo*-8-anti-4[-(3-trifluoromethylphenoxi)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan, 2.5 mL 1,3-propanediol, 190 mg TsOH·H_2O, 4.5 mL anh. THF; PC (eluent: ethyl acetate-hexanes, 1:1); a pure fraction of 252 mg (54.2%) product **18c** was obtained as oil, $[\alpha]_D$ = -17.96°(1% in THF), IR: 3366br s, 2958s, 2930s, 2875s, 1715s, 1624m, 1493w, 1455m, 1327vs, 1290m, 1227m, 1167s, 1125s, 1097m, 1044s, 980m, 876w, 790w, 697w, ^{1}H-NMR-300MHz ($CDCl_3$, *ä* ppm, *J* Hz): 7.39 (t, 1H, H-5", 8.0), 7.24 (dd, 1H, H-4", 2.2, 8.0), 7.13 (t, 1H, H-2", 1.9), 7.06 (dd, 1H, H-6", 2.2, 8.0), 6.93 (dd, 1H, H-13, 8.5, 15.7), 6.44 (d, 1H, H-14, 15.7), 4.79 (s, 2H, H-16), 4.25 (q, 1H, H-11, 6.8), 4.16 (q, 1H, H-9, 6.8), 4.15 (t, 2H, 3', 6.3), 3.65 (t, 2H, H-1', 6.6), 2.89 (br s, 2H, OH), 2.59-2.38 (m, 4H, H-8, 2H-7', H-12), 2.28 (t, 2H, H-10, 8.8), 1.83 (m, 2H, H-2', 6.0), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 194.57 (C-15), 171.88 (C-6'), 157.93 (1"), 148.40 (C-13), 132.07 (q, C-3", *J* = 32.2Hz), 130.33 (C-5"), 126.85 (C-14), 123.85 (q, CF_3, *J* = 271.6Hz), 118.55 (d, C-4", *J* = 3.7Hz), 118.13 (C-2"), 111.83 (q, C-6", *J* = 3.5Hz), 74.83 (C-11), 71.94 (C-16), 61.95 (C-3'), 59.60 (C-9), 59.00 (C-1'), 56.31 (C-12), 50.14 (C-8), 44.12 (C-10), 35.72 (C-7'), 31.43 (C-2').

5-hydroxypentyl 2-((1R,2R,3R,5R)-5-chloro-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, 20a (X = Cl, Hlg = Cl).

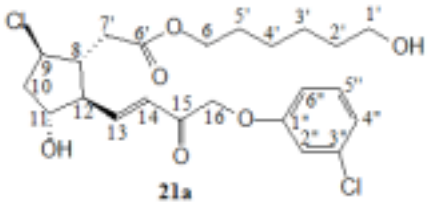


20a

1.42 g (4 mM) (±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan, 10 mL 1,5-pentanediol, 0.7 g TsOH·H_2O, 10 mL anh. THF + 20 mL CH_2Cl_2; TLC (Silica

gel, toluene-ethyl acetate, 1:1, $R_{f\,in}$ =0.62, $R_{f\,product}$ 0.31); 2.5 g crude product; crystallyzed from ethyl ether-heptane, 1.25 g (57.3%) of pure compound **20a** were obtained, m.p. = 63-65°C (twice recrystallized), elemental analysis, calctd. for $C_{22}H_{28}Cl_2O_6$: th.(%): Cl: 15.44; found (%): Cl: 15.40, IR (2% în $CHCl_3$) : 3030, 2920, 2910, 1715-1705, 1615, 1585, 1470, 1270, 1250.

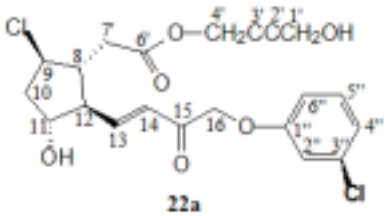
5-hydroxyhexyl 2-((1R,2R,3R,5R)-5-chloro-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, 21a (X = Cl, Hlg = Cl).



21a

1.42 g (4 mM) (±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan, 11.8 g 1,6-hexanediol, 0.76 g $TsOH{\cdot}H_2O$, 50 mL anh. THF + 30 mL CH_2Cl_2; TLC (Silica gel, toluene-ethyl acetate, 1:1, $R_{f\,in}$ =0.62, $R_{f\,product}$ 0.33); PC (eluent: ethyl acetate-heptane, 1:1); a pure fraction of 1.2 g (63.4%) compound **21a** was obtained as oil, IR: 3450-3350, 2930, 2860, 1730, 1625, 1600, 1470, 1285, 870.

(±)-4-hydroxy-2-but-2-yn-1-yl 2-((1R,2R,3R,5R)-5-chloro-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, 22a (X = Cl, Hlg = Cl).

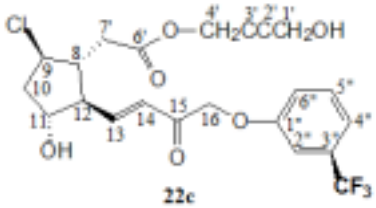


22a

353 mg (1 mM) (±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan, 2.5 mL 2-butyne-1,4-diol, 190 mg $TsOH{\cdot}H_2O$, 2.5 mL anh. THF + 4.5 mL CH_2Cl_2; PC (eluent: ethyl acetate-hexanes, 1:1); 200 mg (45.3%) of pure product **22a** were obtained as oil,

^{1}H-NMR-300MHz ($CDCl_3$, δppm, *J* Hz): 7.15 (t, 1H, H-5", 8.2), 6.92 (ddd, 1H, H-4", 1.1, 1.9, 8.2), 6.85 (t, 1H, H-2", 1.9), 6.84 (d, 1H, H-13, 15.7), 6.73 (ddd, 1H, H-6", 1.1, 2.5, 8.2), 6.41 (d, 1H, H-14, 15.7), 4.70 (s, 2H, H-16), 4.62 (s, 2H, H-4'), 4.24 (q, 1H, H-11, 6.8), 4.19 (s, 2H. H-1'), 4.16 (q, 1H, H-9, 6.8), 2.57 (dd, 1H, H-7', 3.6, 14.6), 2.40 (dt, 1H, H-7', 6.9, 14.8), 2.38-2.35 (m, 2H, H-8, H-12), 2.25 (dd, 2H, H-10, 6.4, 6.8), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 195.01 (C-15), 170.80 (C-6'), 158.46 (1"), 148.09 (C-13), 135.19 (C-3"), 130.61 (C-5"), 127.41 (C-14), 122.20 (C-4"), 115.33 (C-6"), 113.23 (C-2"), 85.69 (C-3'), 79.26 (C-2'), 74.96 (C-11), 71.96 (C-16), 59.26 (C-9), 56.27 (C-12), 52.50 (C-4'), 50.88 (C-1'), 50.28 (C-8), 44.04 (C-10), 35.18 (C-7').

(-)-4-hydroxy-2-but-2-yn-1-yl 2-((1R,2R,3R,5R)-5-chloro-3-hydroxy-2-((E)-3-oxo-4-(3-(trifluoromethyl) phenoxy)but-1-en-1-yl)cyclopentyl)acetate, 22c (X = CF_3, Hlg = Cl)

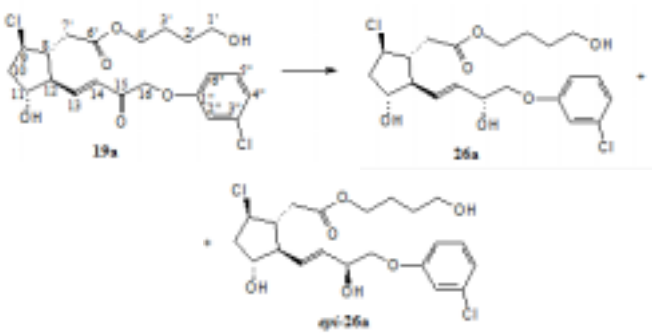


22c

353 mg (1 mM) (-)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-trifluoromethylphenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo[3.2.1]octan was reacted and purified as in 10. A pure fraction of 185 mg (39%) pure product **22c** was obtained as oil, $[\alpha]_D$ = -14.27°(1% în THF),

IR (oil in ATR): 3399br m, 2934w, 2251w, 1735s, 1623m, 1595w, 1493w, 1453m, 1326vs, 1288m, 1226m, 1165s, 1122vs, 1064s, 1021s, 975m, 909m, 875w, 790w, 697m, 653m, ^{1}H-NMR-300MHz ($CDCl_3$, δ ppm, *J* Hz): 7.35 (t, 1H, H-5", 8.2), 7.19 (m, 1H, H-4"), 7.08 (m, 1H, H-2"). 7.01 (dd, 1H, H-6", 2.5, 8.2), 6.97 (dd, 1H, H-13, 8.5, 15.7), 6.42 (d, 1H, H-14, 15.7), 4.76 (s, 2H, H-16), 4.61 (s, 2H, H-4'), 4.24 (q, 1H, H-11, 6.8), 4.18 (t, 2H. H-1', 1.6), 4.18 (q, 1H, H-9, 6.8), 2.71 (br s, 2H, OH), 2.56 (dd, 1H, H-7', 4.4, 14.8), 2.40 (dt, 1H, H-7', 6.9, 14.8), 2.38-2.35 (m, 2H, H-8, H-12), 2.25 (br t, 2H, H-10, 6.8), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 194.70 (C-15), 170.83 (C-6'), 157.89 (1"), 148.22 (C-13), 132.12 (d, C-3", *J* = 32.6Hz), 130.39 (C-5"), 127.38 (C-14), 123.87 (q, CF_3, *J* = 272.6Hz), 118.81 (q, C-4", *J* = 3.6Hz), 118.20 (C-6"), 111.80 (q, *J* = 3.6Hz, C-2"), 85.65 (C-3'), 79.23 (C-2'), 74.93 (C-11), 71.90 (C-16), 59.25 (C-9), 56.36 (C-12), 52.46 (C-4'), 50.81 (C-1') 50.26 (C-8), 44.04 (C-10), 35.16 (C-7').

4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-2-((R,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-3-hydroxycyclopentyl)acetate 26a and 15-*epi* isomer, 4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-2-((S,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-3-hydroxycyclopentyl)acetate *epi*-26a (X = Cl, Hlg = Cl).



19a 26a epi-26a

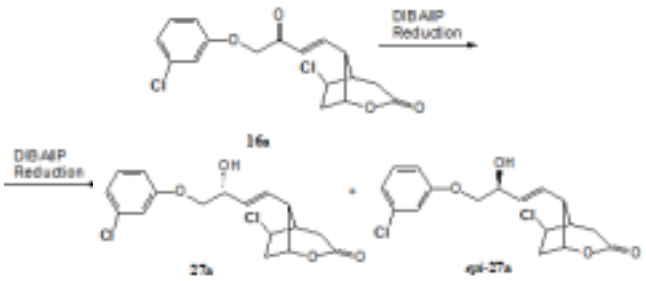
4.45 g (10 mM) 4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-2-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-3-hydroxycyclopentyl)acetate were dissolved in 15 mL pyridine, cooled on an ice-bath, 5.5 mL trimethylchlorosilane was added dropwise under stirring and the reaction mixture stirred overnight. Ethyl ether (80 mL) was added, the reaction mixture was poured under efficient stirring over 50 mL 10% $KHCO_3$ solution, the phases were separated (Aqueous phase extracted with 15 mL ethyl ether), organic phase dried ($MgSO_4$), filtered, concentrated and coevaporated with toluene (50 mL). The crude product was dissolved in toluene (50 mL) and THF (15 mL), the solution was cooled to -78°C under inert argon, 80 mL 0.25M diisobornyloxyaluminiumizopropoxide in toluen was slowly added and the mixture was stirred until the starting enone reacted (TLC monitoring). 25 mL 10% H_2SO_4 soln. was added, the cooling bath was removed, stirred one hour, ethyl acetate 50 mL) added, phasess separated (aqueous phase extracted with ethyl acetate), organic phase dried ($MgSO_4$), concentrated and the crude product purified by PC (eluent: extraction benzine until elution of isoborneol, then benzene-acetone, 4 : 1). 1.80 g (40.2%) pure *epi*-isomer, ***epi*-26a**, 4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-2-((S,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-3-hydroxycyclopentyl)acetate, as oil:

***epi*-26a:** ^{1}H-NMR-300MHz ($CDCl_3$, δ ppm, *J* Hz): 7.20 (t, 1H, H-5", 8.2), 6.95 (dd, 1H, H-4", 2.2, 8.2), 6.91 (t, 1H, H-2", 2.2), 6.80 (dd, 1H, H-6", 2.2, 8.2), 5.74 (dd, 1H, H-14, 7.7, 15.4), 5.67 (dd, 1H, H-13, 5.5, 15.4), 4.50 (dt, 1H, H-15, 3.9, 7.7), 4.17 (t, 1H, H-11, 8.0), 4.14 (t, 1H, H-9, 6.8), 4.12 (t, 2H, H-4', 6.3), 3.96 (dd, 2H, H-16, 3.9, 9.3), 3.87 (dd, 1H, H-16, 7.7, 9.3), 3.66 (t, 2H. H-1', 6.3), 2.57 (dd, 1H, H-7', 5.5, 15.4), 2.46 (dt, 1H, H-7', 6.6, 15.4), 2.27 (br dt, 2H, H-10, 8.0, 6.8), 2.32-2.16 (m, 2H, H-8, H-12), 1.72 (cv, 2H, H-3', 6.3), 1.63 (cv, 2H, H-2', 6.3), ^{13}C-NMR-75MHz ($CDCl_3$, δppm): 172.13 (C-6'), 159.26 (1"), 135.06 (C-3"), 133.04 (C-13), 131.31 (C-14), 130.50 (C-5"), 121.60 (C-4"), 115.16 (C-6"), 113.26 (C-2"), 75.21 (C-11), 71.94 (C-16), 70.45 (C-15), 64.73 (C-4'), 62.35 (C-1'), 59.71 (C-9), 56.56 (C-12), 50.37 (C-8) 35.69 (C-7'), 29.16 (C-2'), 25.19(C-3').

and 1.75 g (39.1%) pure product **26a** were obtained as oil,

26a: ^{1}H-NMR-300MHz ($CDCl_3$, δ ppm, *J* Hz): 7.21 (t, 1H, H-5", 8.2), 6.96 (dd, 1H, H-4", 2.2, 8.2), 6.92 (t, 1H, H-2", 2.2), 6.86 (dd, 1H, H-6", 2.2, 8.2), 5.78 (dd, 1H, H-14, 8.0, 15.4). 5.65 (dd, 1H, H-13, 4.5, 15.4), 4.56 (m, 1H, H-15), 4.21-4.08 (m, 2H, H-9, H-11), 4.14 (t, 2H, H-4', 6.3), 3.97 (dd, 2H, H-16, 3.6, 9.6), 3.87 (dd, 1H, H-16, 7.7, 9.6), 3.67 (t, 2H. H-1', 6.3), 2.55 (dd, 1H, H-7', 5.5, 15.4), 2.45 (dt, 1H, H-7', 6.3, 15.4), 2.28 (br t, 2H, H-10, 6.9), 2.36-2.16 (m, 2H, H-8, H-12), 1.72 (q, 2H, H-3', 6.3), 1.64 (q, 2H, H-2', 6.3), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 171.91 (C-6'), 159.45 (1"), 135.07 (C-3"), 133.27 (C-13), 131.12 (C-14), 130.50 (C-5"), 121.63 (C-4"), 115.16 (C-6"), 113.26 (C-2"), 75.20 (C-11), 71.96 (C-16), 70.49 (C-15), 64.67 (C-4'), 62.43 (C-1'), 59.70 (C-9), 56.68 (C-12), 50.58 (C-8), 35.75 (C-7'), 29.18 (C-2') 25.20 (C-3').

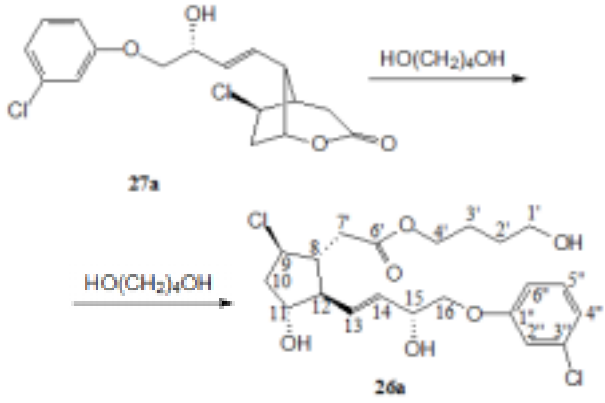
(±)-6-chloro-8-((R,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-2-oxabicyclo[3.2.1]octan-3-one 27a and (±)-6-chloro-8-((S,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-2-oxabicyclo[3.2.1]octan-3-one, *epi*-27a.



353 mg (1 mM) (±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3-oxo-1-trans-butenyl]-2-oxabicyclo [3.2.1]octan were reduced and the crude product purified in the conditions presented at point 12. The pure compound **27a** was obtained as oil (145 mg, 40.8%), ^{1}H-NMR-400MHz (DMSO-d_6, δppm, *J* Hz): 7.33 (t, 1H, H-5", 8.2), 7.00 (m, 1H, H-4"), 6.97 (dd, 1H, H-2",0.8, 2.2), 6.92 (dd, 1H, H-6", 2.2, 8.2), 5.94 (ddd, 1H, H-13, 1.1, 7.0, 15.7), 5.81 (m, 1H, H-14, 15.7), 5.30 (d, 1H, OH, 4.1), 4.74 (m, 1H, H-1), 4.60 (dd, 1H, H-6, 4.3, 8.0), 4.33 (q, 1H, H-15, 5.3), 3.93 (dd, 1H, H-16, 4.9, 10.0), 3.88 (dd, 1H, H-16, 6.4, 10.0), 3.06 (d, 1H, H-8, 7.0), 2.93 (dd, 1H, H-4, 5.6, 18.7), 2.88 (m, 1H, H-7, 7.6, 17.2), 2.70 (dd, 1H, H-4, 1.6, 18.7), 2.59 (m, 1H, H-5), 2.34 (m, 1H, H-7, 17.2), ^{13}C-NMR-100MHz ($CDCl_3$, δ ppm): 167.95 (C-6'), 159.40 (1") 133.55 (C-3") 132.78 (C-13), 130.69 (C-5"), 127.78 (C-14), 120.37 (C-4"), 114.53 (C-2"), 113.51 (C-6"), 83.58 (C-1), 71.93 (C-15), 68.84 (C-9), 60.00 (C-6), 48.95 (C-5 or 8), 47.16 (C-8 or 5), 43.80 (C-7), 38.83 (C-4).

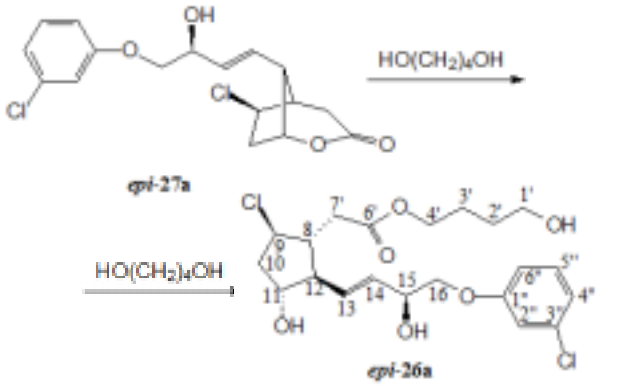
The compound ***epi*-27a** was obtained impure as oil and was used in the next reaction with 1,4-butanediol.

4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-2-((R,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-3-hydroxycyclopentyl)acetate 26a.



178 mg (0.5 mM) (±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3α-hidroxy-1-trans-butenyl]-2-oxabicyclo[3.2.1]-octan **27a** were reacted in the conditions presented at pct. 1 with 90 mg $TsOH \cdot H_2O$, 2.5 mL 1,4-butanediol, 2 mL anh. THF, resulting 165 mg (93%) halogenated prostaglandin compound **26a** as oil, with the same characteristics as that presented at point 12.

4-hydroxybutyl 2-((1R,2R,3R,5R)-5-chloro-2-((S,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-3-hydroxycyclopentyl)acetate *epi*-26a.

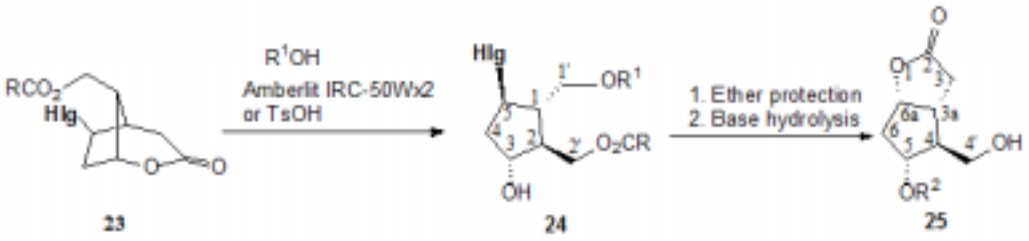


An impure fraction of 267 mg (0.5 mM) (±)-*exo*-6-chloro-3-*exo*-8-anti-4[-(3-chlorophenoxy)-3β-hidroxy-1-trans-butenyl]-2-oxabicyclo[3.2.1]-octan ***epi*-27a** with 3α-hydroxy compound **27a** was treated with 140 mg $TsOH \cdot H_2O$, 3.8 mL 1,4-butanediol, 3 mL anh. THF, resulting after PC purification of the crude product 165 mg halogenated prostaglandin ***epi*-26a** as oil, with the same characteristics as that presented at pct. 12 and 58 mg of **26a**.

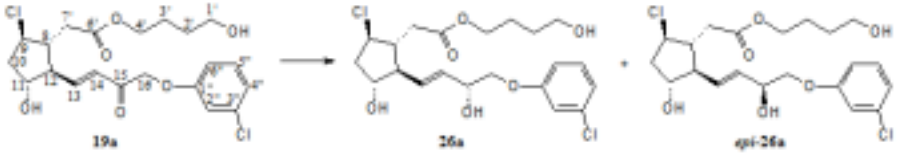
Results and disscusions

In a previous paper [9] we presented the transformation of a γ-lactone intermediate **23** into a Corey γ-lactone intermediate **25** by a sequence of high yield reactions in which the first one is an acid catalyzed opening of δ-lactone with alcohols (with methanol, for R = C_6H_5 the reaction is quantitative) (scheme 7.):

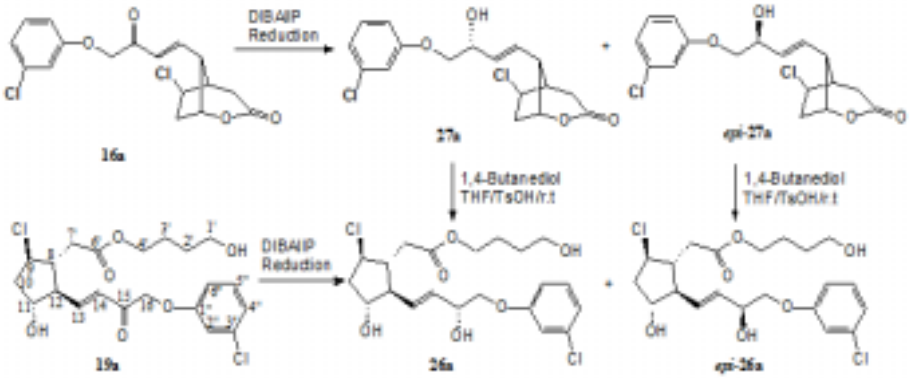
These good results determined us to study other reactions for opening of a δ-lactone skeleton with diols and in this paper we present acid catalyzed opening of enones **16** with diols to the 9β-halogenated prostaglandin



Scheme 7. Transformation of δ-lactone alcohol **23** into Corey γ-lactone **25**



Scheme 8. Reduction of 9β-prostaglandin analogue **19a** with diisobornyloxy-aluminium isopropoxide to the allylic alcohols **26a** and *epi* - **26a**



Scheme 9. The two routes for obtaining 15α - and 15β-hydroxy-9β-chloro-prostaglandin analogues 26a and *epi*-**26a**

analogues **17-22** (scheme 6); an unsaturated diol, 2-butyne-1,4-diol, was also used as diol. These compounds have an ester group in the position 6 of prostaglandin á-side chain and an alcohol group instead of C-1 carboxyl group spaced by two to 6 methylene groups from the oxygen of the ester group.

The enones **16** used in this study have as substituent in the 3-position of phenoxy-group a chlorine atom or a trifluoromethyl group and as halogen on the lactone ring an *exo*-chlorine or *exo*-bromine atom and these enones are racemic or optically active compounds.

We used $TsOH \cdot H_2O$ as catalyst and as diols ethylene glycol to 1,6-hexanediol alone or in the presence of an inert solvent like THF; the reactions were performed at room temperature by stirring overnight and monitoring the reactions by TLC. Best results were obtained for 1,4-butanediol and the α-side chain of this prostaglandin analogue mimics the length of prostaglandins α-side chain, but having a hydroxyl group instead of a carboxyl one. The compounds **19a**, **19b** and **20a** were obtained crystallyzed (**19a** and **20a** were crystalized from the crude product), the others ones were obtained as oils.

The prostaglandin analogues **17-22** maintain the 15-keto group presented in the starting δ-lacton-enone **16**; in the literature there are numerous prostaglandin analogues with a 15-keto group investigated for different biological activities.

But natural prostaglandins and their analogues have a 15α-OH group, instead of 15 keto group. So we reduced the 15-keto group, after protection of 11-OH group and also of terminal hydroxyl as trimethylsilyl, with the reagent used by us for the reduction of 16-phenoxy- or 16-(3-substituted)phenoxy prostaglandin intermediates: diisobornyloxyaluminium isopropoxide (DIBAlP) as 0.2-0.25M solution in toluene at low temperature (<-70°C) (scheme 8) [10]. The selectivity of the reduction was smaller that that obtained for reduction of 15-keto group of the corresponding γ-lactone intermediates with ω-side chain (~84% 15α-isomer).

The allylic alcohols were separated by pressure chromatography and were obtained as oils. The reduction of the enone **19a** with sodium borohydride in the presence of $CeCl_3 \cdot 7H_2O$ [11] or Dowex 1×8 [12] was also not selective, the allylic alcohols **26a** and ***epi*-26a** being obtained in about 1:1 ratio.

We realized also the reduction of the ä-lacton-enone **16a** with the same reagent DIBAlP (in this case there is necessary no trimethylsilyl protection, because the hydroxyl group is blocked in the lactone group) and it was observed that also in this case the reduction of the enone group is not different in selectivity from the reduction of enone **19a**; the allylic alcohols **27a** and ***epi*-27a** were obtained also in about 1:1 ratio (scheme 9). Allylic alcohols **27a** and ***epi*-27a** were separated by pressure chromatography and were used in the reaction with 1,4-butanediol in the same conditions as that used for δ-lacton-enone **16a** and we obtained 9β-chloro-15α-hydroxy prostaglandin analogue **26a** and its epimer 15-hydroxy, ***epi*-26a**. A patent pending was fulfield on these works [13].

The new prostaglandin analogues were characterized by elemental analysis, optical rotation for optically active compounds, IR, ^1H- ^{13}C- and 2D-NMR spectra.

The new compounds are to be tested for their biological activity and the results will be published separatelly.

Conclusions

A number of new 9βϖ-halogeno-(chloro or bromo)-15-ketoprostaglandin analogues with a 16-(3-chloro- or 3-trifluoromethyl)phenoxy fragment in ω-side chain were synthesized. The compounds contains an ester group at the carbon atom 6 of α-side chain with diols, $HO(CH_2)_nOH$ with n = two to 6, or 2-butyne-1,4-diol. Some of the 15-keto-prostaglandin analogues were reduced with DIBAlP at low temperature (<-70°C) as we realized for 16-

phenoxy-γ-lactone-intermediates and also with other reducing reagents based on $NaBH_4$, but in all cases the reduction was not selective, the allylic alcohols **26a** and ***epi*-26a** being obtained in a ratio of about 1:1.

An earlier reduction of enone group of starting prostaglandin intermediate **19**, realized in the same reaction conditions, was also non-selective, the allylic alcohols **27a** and ***epi*-27a** being obtained also in a ratio of about 1:1.

Both allylic alcohols **27a** and ***epi*-27a** were then opened with 1,4-butanediol, in the same reaction conditions as for δ-lacton-enone **16a**, and obtained the same allylic alcohols **26a** and ***epi*-26a**.

All the new 9β-halogeno-prostaglandin analogues were characterized by elemental analysis, IR, ^{1}H- ^{13}C- and 2D-NMR. The biological activity of the compounds will be presented separatelly.

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