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Mendeleev Commun., 2017, **27**, 125–127
Mendeleev Communications

Side-modified 15-deoxy-$\Delta^{12,14}$-prostaglandin D_2, precursor of corresponding PGJ_2. Synthesis from cloprostenol and anticancer activity

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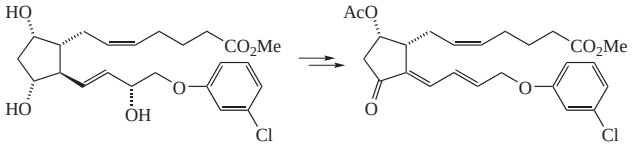
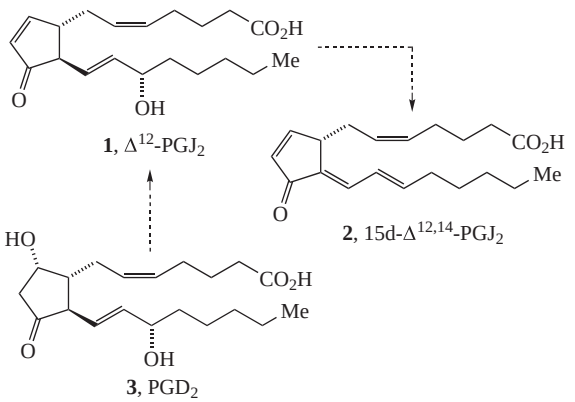
DOI: 10.1016/j.mencom.2017.03.005

The title compound, a possible precursor of metabolically stable corresponding PGJ_2, was obtained from cloprostenol in seven steps. The compound demonstrated cytotoxicity against the HEK 293, Hep G2 and Jurkat cell lines.



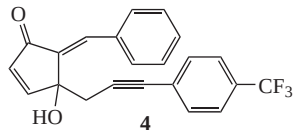
In the series of cyclopentenone prostaglandins (PGs), endogenous Δ^{12}-prostaglandin J_2 **1** and 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 **2** (15d-$\Delta^{12,14}$-PGJ_2) (Scheme 1) attract attention due to their powerful anticancer and antiviral properties.[1–3] The cross-conjugated dienone system in their molecules is responsible for bioactivity.[4] Cyclopentenone-based PGs, **1** in particular, readily penetrate the cell membrane. As highly reactive electrophilic Michael acceptors, they selectively (and reversibly) bind with sulfhydryl groups of glutathione and cysteine in nucleus proteins and thus inhibit the cell cycle, replication of viruses, *etc.*[5,6] Furthermore, 15d-$\Delta^{12,14}$-PGJ_2 **2** promotes the growth of neurites in PCl2 cells and is known as a ligand for PPARγ nucleus receptors responsible for gene transcription, initiation of inflammatory processes, hypertension, apoptosis, *etc.*[7–9] Prostaglandins **1** and **2** are formed in living organisms upon albumin catalyzed metabolism of prostaglandin D_2 **3**.[10]

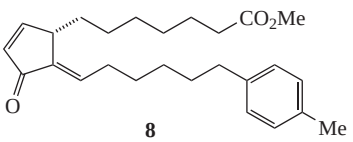


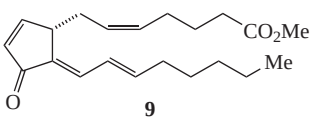
Scheme 1

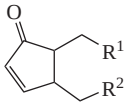
To study the structure–activity relationship (SAR), many analogues of **1** and **2** with simpler structures (Figure 1) were synthesized. For example, Takahashi group synthesized libraries of α,ω-modified cross-conjugated dienones with clavulone topology.[11] The cytotoxicity of twelve of the 76 synthesized analogues was comparable to those of adriamycin in five lines of cancer cells (see, *e.g.*, **4** – the typical structure of a compound of this series). To obtain analogues of compound **2**, Uchida and Takahashi synthesized sixteen compounds, and one of them, the racemic conjugated cyclopentenone **5**, showed neurite growth promotion comparable to that of **2**.[12] Of practical interest is the analogue of **1**, the cross-conjugated cyclopentenone **6** (TEI-9826), which is being studied as a possible anticancer agent.[13] Furthermore, remarkable neuroprotective properties of **6** were also noted.[14] Suzuki *et al.* obtained a more active than TEI analogue **7** (NEP 11) serving as a long-term therapeutic agent against neurodegenerative diseases.[6] Mikołajczyk *et al*. studied *in vitro* cytotoxicity of NEP 11 and its J-type derivative **8**.[15] Previously we reported a synthesis of methyl ester (±)-15d-$\Delta^{12,14}$-PGJ_2 **9** from the racemic Corey lactone diol.[16]

In general, all these biologically active compounds contain cross-conjugated methylidenecyclopentenone fragment which performs the role of pharmacophore and various side chains. In the field of classic prostaglandins, the transformation of the side chains







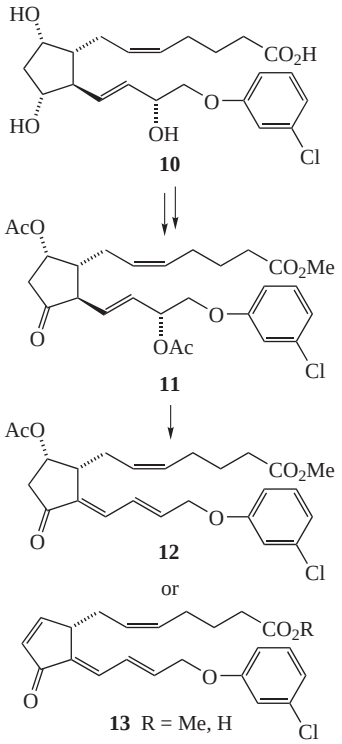


5 R^1 = (*E*)-CH=CHMe, R^2 = (*Z*)-CH=CH$(CH_2)_3$Ph

6 $R^1 = (CH_2)_5CO_2Me$, $R^2 = (CH_2)_6Me$

7 (NEP 11) $R^1 = (CH_2)_5CO_2Me$, R^2 = 4-$MeC_6H_4(CH_2)_5$

Figure 1 Structures of known bioactive analogues of PGJ_2.



Scheme 2 The plan of the synthesis.

has also been widely attempted and led to much more active and metabolically-stable derivatives which have found use as medical drugs. One of them is cloprostenol **10**, a well-known analogue of prostaglandin $F_{2\alpha}$ (Scheme 2). The purpose of this study was to develop a method for the direct conversion of F-type prostaglandins into the cross-conjugated cyclopentenones using cloprostenol **10** as a typical modified prostaglandin. Cloprostenol could be easily obtained by the reported procedure.[17]

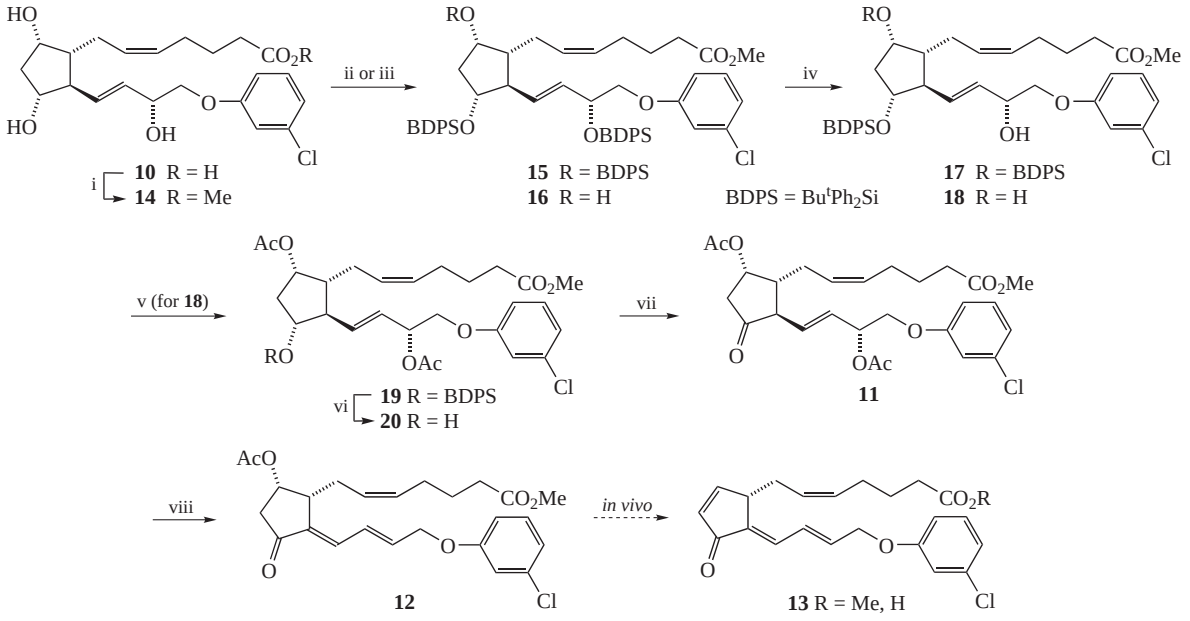
The plan of the synthesis consisted in a differentiation of three secondary hydroxyl groups of cloprostenol to obtain ketone **11**. 11-Carbonyl group in this intermediate will hopefully make amendable 9- and 15-acetoxy functions for an easy mono- or bis-elimination(s) thus resulting in the desired dienones **12** or **13**.

Silylation of cloprostenol methyl ester **14** (Scheme 3) with an excess of Bu^tPh_2SiCl resulted smoothly in tris-ether **15**, but limiting the amount of the silyl chloride to 2.5 equiv. afforded 11,15-bis-ether **16** in good yield. Both silyl polyethers deblocked selectively allylic 15-OH group by the action of 1 equiv. of fluoride ion to give derivatives **17** and **18**.

Diol **18** was found to be optimal for the continuation of the synthesis. The corresponding diacetate **19** was easily desilylated into hydroxy diacetate **20** whose single hydroxyl group was oxidized with PCC into carbonyl group producing the key compound **11**. At the final stage, PGD-type structure **11** was converted to the target compound **12** by keeping it for 12 h with DBU in benzene solution.

The structure of compound (12*E*,14*E*)-**12** was determined by ^1H and ^{13}C NMR spectroscopy using standard 2D techniques: ^1H–^1H COSY, HSQC, HMBC, and NOESY. The main problem was to determine the configuration of the double bonds in the 1,3-diene moiety of the molecule. The value 16 Hz of the coupling constant between protons C^{14}–H (δ 6.42) and C^{15}–H (δ 7.38) confirms their mutual *trans* arrangement. The (*E*)-configuration of 12,13-double bond in **12** was based on NOESY data containing cross-peaks between the protons C^8–H (δ 3.16) and C^{14}–H. According to ^1H–^1H COSY data, proton C^{13}–H (δ 6.23) has long-range correlation with protons C^{10}–H_2 but none with C^{14}–H. We explain the absence of a coupling between C^{13}–H and C^{14}–H as a result of steric hindrance in side chains that causes rotation around the C^{13}–C^{14} bond to reach a 90° angle between the protons at C^{13} and C^{14}. Previously, we noted similar facts of steric hindrance in our studies on syntheses of 16-perfluoronaphthyloxyprostaglandins.[18] Molecular mechanic calculations (semi-empirical method PM6) estimated the distance between protons C^8–H and C^{14}–H as 2.5 Å (*i.e.* NOE is possible) in the conformer of (12*E*,14*E*)-**12** with a H–C^{13}–C^{14}–H dihedral angle ~90° (Figure 2). The same distance in (12*Z*,14*E*)-isomer was calculated to be 4.2 Å, which is clearly too long for the NOE effect.

Prostaglandin **12** was subjected to *in vitro* cytotoxicity tests using MTT assay.[19] The compound demonstrated moderate cytotoxicity in conditionally normal and cancer cell lines with IC_{50} values (48 h) of 19.6 μM for HEK 293 cells, 26.1 μM for Hep G2 cells and 34.4 μM for Jurkat cell line. Obviously, for enhancing the cytotoxic activity[5,14] it is necessary to introduce an endocyclic



Scheme 3 *Reagents and conditions:* i, MeI, K_2CO_3, acetone, room temperature, 20 h, 77%; ii, BDPSCl (5 equiv.), imidazole (6 equiv.), CH_2Cl_2, room temperature, 48 h, 94%; iii, same as ii, but 2.5 equiv. of BDPSCl, 73%; iv, Bu_4NF (1 equiv.), THF, 10 °C, 48 h, 80%; v, Ac_2O, Py, DMAP, CH_2Cl_2, room temperature, 10 h, 86%; vi, Bu_4NF, THF, 10 °C, 24 h, 94%; vii, PDC, CH_2Cl_2, room temperature, 12 h, 77%; viii, DBU, C_6H_6, room temperature, 45%.

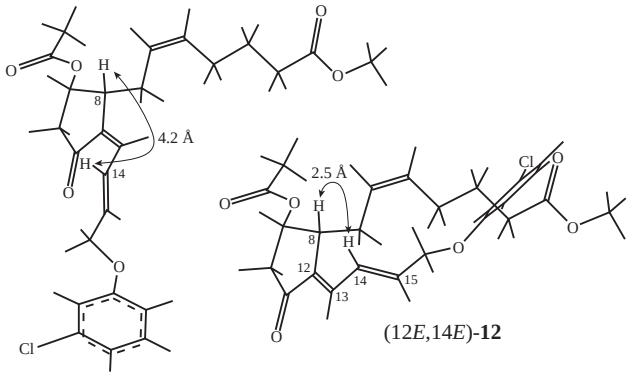


Figure 2 Calculated preferred conformations of compound (12*E*,14*E*)-**12** and its possible (12*Z*,14*E*)-stereoisomer. Lines end here with H atoms.

double bond into the molecule of **12**. We considered compound **12** as a prodrug, since *in vivo* ester hydrolysis and elimination of AcOH from **12** should generate acid **13**, an analoque of compound **2** with a metabolically 'reinforced' ω-chain.

In conclusion, we suggest a practical variant for conversion of F-type prostaglandins into 15-deoxy-$\Delta^{12,14}$-PGD_2 derivatives for cloprostenol **10** as an example. The resulting compound **12** is of obvious pharmacological interest as a precursor of the corresponding analogue of J-type PG **13**. The synthetic scheme includes seven simple stages with an overall yield 12.5% and it is deemed to be applicable for the other F-type prostaglandins.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2017.03.005.

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Received: 30th June 2016; Com. 16/4974