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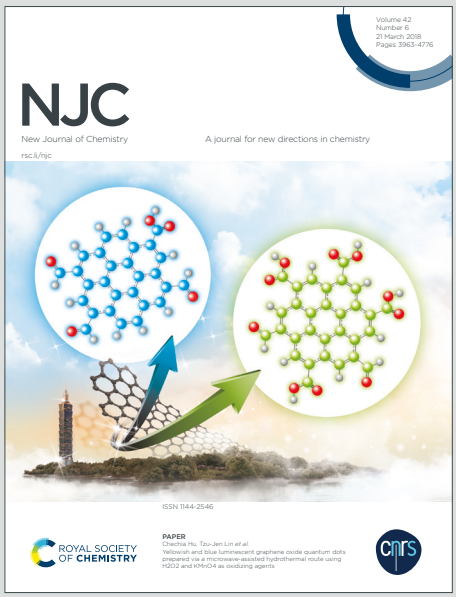

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New β-ketophosphonates for the synthesis of prostaglandin analogues. 2. Phosphonates with bicyclo[3.3.0]octene and bicyclo[3.3.0]octane scaffolds linked to the β-ketone group.

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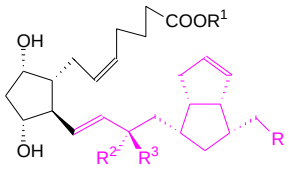
β-Ketophosphonates, with the keto group linked to a bicyclo[3.3.0]oct(a)ene fragment, were synthesized starting from two diacids. These diacids were first transformed into internal anhydride and one into diester. The anhydrides and the diester were reacted with the lithium salt of dimethyl methanephosphonate to give two carboxy β-ketophosphonates, an ester β-ketophosphonate and a bis β-ketophosphonate in good yield. Ester β-Ketophosphonate, obtained by two routes, was used in a E-HEW selective olefination of a prostaglandin aldehyde with α-side chain to give the 15-keto prostaglandin analogue in good yield. The compounds were characterized by elemental analysis, IR and high resolution ^{1}H- and ^{13}C-NMR spectroscopy.

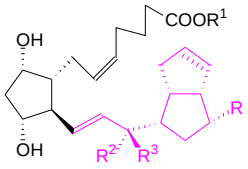
1. Introduction

The vast family of prostaglandins is defined by the structural elements of the cyclopentane ring and the two α- and ω-side chains. The modifications of the α-side chain, the ω-side chain or both were done for designing new prostaglandin analogues, but the most beneficial modifications to the associated biological activities were performed on the ω-side chain. In the total stereo-controlled Corey convergent synthesis of prostaglandins, the ω-side chain is introduced in the molecule by an *E*-selective Horner-Emmons-Wadsworth (HEW) olefination of an aldehyde, with a δ-lactone, γ-lactone and cyclopentane structure (at different steps of the reaction sequence), with a β-ketophosphonate, in the presence of a base. Therefore, the design of the ω-side chain of the target prostaglandin molecule is integrated in the design of the β-ketophosphonate intermediate to be synthesized. A bicyclo[3.3.0]octane fragment is encountered in many natural products, some of them with anticancer activity [1], however, as far as we know, there is no mention in the literature of a bicyclo[3.3.0]octane (octahydropentalene) or bicyclo[3.3.0]octene (hexahydropentalene) fragment used in prostaglandin analogues. In our works in the field we aim to create new prostaglandin analogues with this fragment in the ω-side chain and the first step in this direction is to synthesize the key β-ketophosphonates intermediates, used in their convergent synthesis.

Previously we synthesized β-ketophosphonates with a bicyclo[3.3.0]octene scaffold spaced by a methylene group from the β-ketone [1] to obtain prostaglandin analogues of type **I** in which "the bicyclo[3.3.0]octene fragment is spaced far enough from C_{15}, not to hinder the access of the PG-receptor to the functional group linked to C_{15} carbon atom; at the same time, the new bicyclo[3.3.0]octene fragment is enough spaced to contribute to the biological activity of the new prostaglandin analogues" [1].



I. Prostaglandin analogues with a bicyclo[3.3.0]octene fragment in the ω-side chain



II. Prostaglandin analogues with a bicyclo[3.3.0]oct(a)ene fragment in the ω-side chain linked to C_{15} carbon atom

Figure 1. Prostaglandin analogues with a bicyclo[3.3.0]octene fragment spaced from the C_{15} carbon atom by a methylene group (**I**) and a bicyclo[3.3.0]oct(a)ene fragment linked to the C_{15} carbon atom (**II**).

In this paper we present the synthesis of new β-ketophosphonates with bicyclo[3.3.0]octene and bicyclo[3.3.0]octane scaffolds linked to the β-ketone group, to give more restricted access to the C_{15} carbon atom from the ω-side chain of the prostaglandin analogues of type **II**, and the synthesis of one prostaglandin analogue with this fragment in the ω-side chain. The main theme of the work is to search for new metabolically and chemically more stable and active analogues of prostaglandins.

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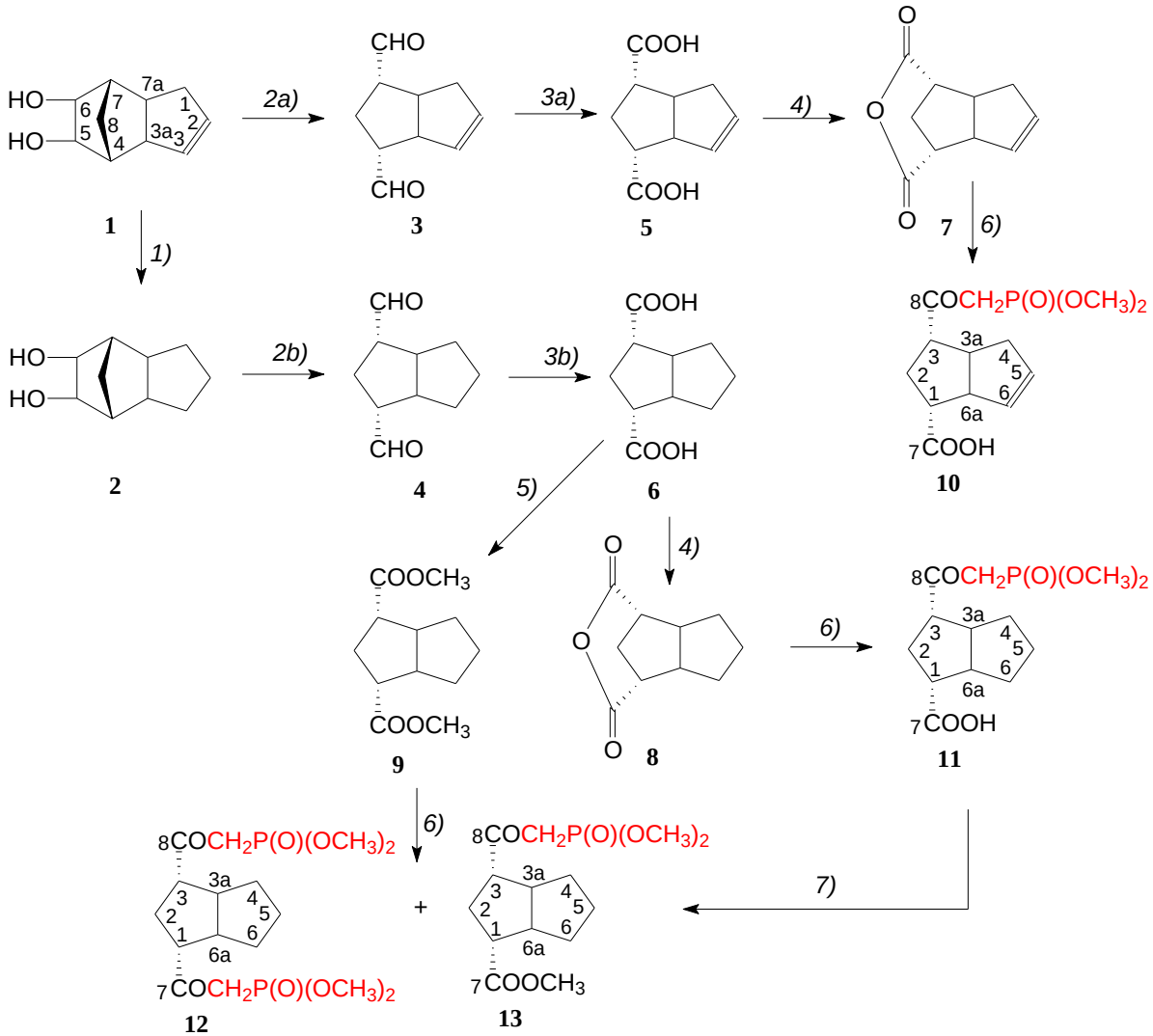
2. Results and discussion

For the synthesis of new β-ketophosphonates, we choose as a key step the reaction of an ester with dimethyl methanephosphonate (DMPh) in the presence of *n*-butyllithium at a reduced temperature (<-70˚C) in anh. THF and the reaction of an anhydride with dimethyl methanephosphonate in the same conditions [2]. The first method is usually used in the Corey procedure of prostaglandin synthesis to obtain the β-ketophosphonates for manufacturing new prostaglandin analogues (for ex.: [3-8]); we used this procedure in the micro-production of prostaglandin analogues and also for obtaining the β-ketophosphonates with a bicyclo[3.3.0]octene fragment in the molecule, which we described in a previous paper [1].

The synthesis of new β-ketophosphonates, with a double bond and a single bond in the cyclopentane ring, is presented in Scheme 1:

Synthesis of the *unsaturated β-ketophosphonate* **10** started from the diacid **5**, obtained by oxidative cleavage of 5,6-dihydroxydicyclopentadiene **1** to dialdehyde **3** [9] followed by Jones oxidation, in 72.5 % yield on two steps. Anhydride **7** was obtained by a published procedure [10] in 81.3 % yield. In the final step, anhydride **7** reacted with the lithium salt of DMPh, which had been obtained by the reaction of DMPh with *n*-BuLi at a reduced temperature (below -70°C), giving the unsaturated β-ketophosphonate **10**, mp, 113-114°C, in 73.5 % yield.

The synthesis of the *saturated β-ketophosphonates* **11**, **12** and **13** started from the same 5,6-dihydroxydicyclopentadiene **1**, which was first hydrogenated (10 % Pd/C, 10 atm. H_2, rt, 97 % yield) to **2**.



Scheme 1. Synthesis of β-ketophosphonates **10**-**13** from di-acids **5** and **6**.

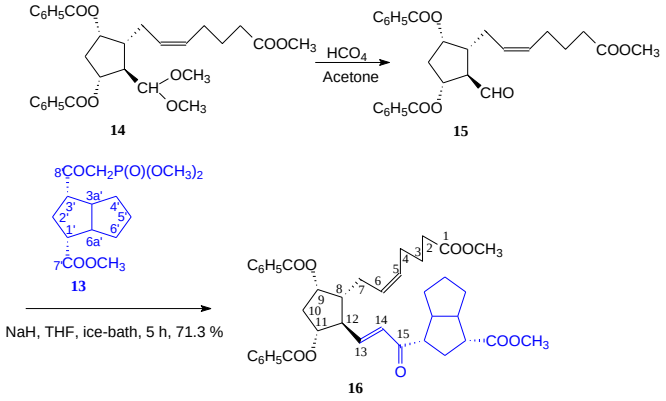
1) H_2 (10 atm), 10% Pd/C, EtOAc, 97%; *2a)* $NaIO_4$, EtOH-water, 0-5˚C; *3a)* 2.44 M Jones reagent, acetone, 0-10˚C, 72.5 % on two steps; *2b)* $NaIO_4$, EtOH-water, 0-5˚C; *3b)* 2.44 M Jones reagent, acetone, 0-10˚C, 72.5 % on two steps; 78.0 %; *4)* Ac_2O, 80-90˚C, 9 h, 81.3 % for **7**, quantitative for **8**; *5)* MeOH, TsOH, overnight, 91.3 %; *6)* dimethyl methanephosphonate, *n*-BuLi, < -65˚C with **7**, 73.5 % **10**; with **8**, 84.1 % **11**; with **9**, 42.0 % **12** and 47.4 % **13**; *7)* CH_2N_2 chloroform-ethyl ether, 92%.

The oxidative cleavage of diol **2**, followed by Jones oxidation of the dialdehyde intermediate **4**, gave the saturated diacid **6** in 78 % yield over two steps. The saturated anhydride **8** was obtained in the same conditions as for **7** in almost quantitative yield. Finally, the reaction of this anhydride with the lithium salt of DMPh gave the crystallized (mp 148-150°C) saturated β-ketophosphonates **11** in 84.1% yield.

For the synthesis of the β-ketophosphonates **12** and **13**, we followed a reaction sequence where we use the diester compound **9** in the final step, as in our previous paper [1]. So, the diacid **6** was esterified with methanol in the presence of TsOH as acid catalyst to the crystallized diester (mp 71-73.0°C) **9** in 91.3 % yield. Then the diester was reacted with 2.05 equivalents of lithium salt of DMPh, giving pure mono β-ketophosphonate **13** in 47.4% yield and bis β-ketophosphonate **12** in 42.0% yield.

Finally, the carboxylic β-ketophosphonate **11** was esterified with diazomethane to the ester phosphonate **13**, obtained previously from diester **9**, giving another confirmation of the structure of both compounds.

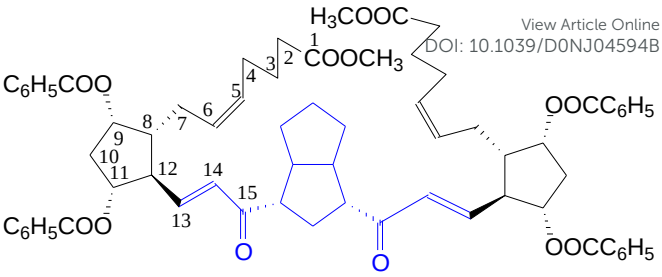
We then tested the *E*-HEW selective olefination of the prostaglandin aldehyde intermediate **15**, obtained by trans-ketalyzation of the dimethylaketal intermediate **14** in acetone, in the presence of 70% $HClO_4$ as catalyst, with the mono β-ketophosphonate **13** (Scheme 2) and obtained the new prostaglandin analogue **16** in 71.3 % yield, as an oil.



Scheme 2. Synthesis of prostaglandin analogue **16** with β-ketophosphonate **13**.

It is worth mentioning that the reduction of the 15-ketone group with aluminium diisobornyloxyisopropoxyde, a reagent used in the selective reduction of 16-aryloxy intermediates (15-keto intermediates for obtaining cloprostenol, fluprostenol, travoprost), gives no 15-allylic alcohol. This shows that the bicyclo[3.3.0]octane skeleton, linked to the C_{15} carbon atom, is bulky enough to block the access of the also bulky reducing reagent. This first reduction of **16** predicts that the usual enzymatic inactivation of prostaglandins, by transforming 15α-OH into 15-keto group, will be hindered by the bulky bicyclo[3.3.0]octane fragment, as we initially assumed.

The use of bis β-keto-phosphonate **12** in the usual HEW olefination conditions should give the *pseudo*-prostaglandin compoud **III**, like we mentioned in the previous paper [1]:



III, 15-keto-*pseudo*-Prostaglandin analogue

Figure 2. 15-Keto-*pseudo*-prostaglandin analogue **III** should be obtained from bis-β-ketophosphonate **12**.

4. Experimental

Melting points (uncorrected) were determined in open capillary on an OpiMelt melting point apparatus. The progress of the reactions was monitored by TLC on Merck silica gel 60 or 60F_{254} plates eluted with the solvent systems: I, benzene-ethyl acetate-hexane, 5:3:2, II, ethyl acetate-hexane-acetic acid, 5:4:0.1, III, ethyl acetate-hexane-acetic acid, 5:1:0.1, IV, hexane-ethyl acetate-acetic acid, 5:2:0.1. Spots were developed in UV and with 15% H_2SO_4 in MeOH (heating at 110˚C, 10 min.). IR spectra were recorded on FT-IR Perkin Elmer spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian 300 MHz spectrometer, chemical shifts are given in ppm relative to TMS as internal standard. Complementary spectra: 2D-NMR and decoupling were done for the correct assignment of the NMR signals. The numbering of the atoms in the compounds is presented in Scheme 1 and Scheme 2. Dialdehyde **3** was obtained as we described in our previous paper [11].

*1. Synthesis of compound **2**.*

100 g (0.6016 mol), (3aS,4R,7S,7aR)-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoindene-5,6-diol, dissolved in ethyl acetate (1L) were hydrogenated on 10% Pd/Cat 10 atmosphere H_2, monitoring the end of the reaction by ^{1}H- and ^{13}C-NMR. The catalyst was filtered off, washed with ethyl acetate used to wash autoclave (TLC monitoring on catalyst washing), the filtrate was concentrated to dryness under reduced pressure, the concentrate co-evaporated with benzene, resulting 97 g (97 %) of crystallized compound **2** in mass. A sample of 11 g was crystallized from benzene-hexane, resulting 9.35 g of pure product **2**, (3aR,4S,7R,7aS)-octahydro-1H-4,7-methanoindene-5,6-diol, crystallized as needles, mp 67.0-68.0 ˚C, ^{1}H-NMR (DMSO-d_6, δppm, *J* Hz):4.47 (s, 2H, OH), 3.73 (m, 2H, H-5, H-6), 2.31 (m, 2H, H-3a, H-7a), 1.90 (dt, 2H, H-4, H-7, 1.5, 5.4), 1.77 (dt, 1H, H-8, 1.7, 9.7), 1.59-1.52 (m, 3H, H-1, H-2, H-3), 1.47-1.21 (m, 3H, H-1, H-2, H-3), 1.15 (dq$_v$, 1H, H-8, 1.5, 9.7), ^{1}H-NMR (DMSO-d_6 +TFA, δppm, *J* Hz): 7.45 (OH moved from 4.47), 3.73 (d, 2H, H5, H-6, 1.9), 2.30 (m, 2H, H-3a, H-7a), 1.90 (dt, 2H, H-4, H-7, 1.5, 5.4), 1.77 (dt, 1H, H-8, 1.7, 9.7), 1.59-1.49 (m, 3H, H-1, H-2, H-3), 1.46-1.20 (m, 3H, H-1, H-2, H-3), 1.14 (dq$_v$, 1H, H-8, 1.5, 9.7), ^{13}C-RMN (DMSO-d_6, δppm): 68.68 (C-5, C-6), 48.32 (C-4, C-7), 43.38 (C-3a, C-7a), 36.41 (C-8), 28.32 (C-2), 26.37 (C-1, C-3).

***2.** Synthesis of saturated diacid **6**,(1R,3S,3aR,6aS)-octahydropentalene-1,3-dicarboxylic acid*

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The hydrogenated compound **2** (91.35 g, 0.543 mol) was dissolved in ethanol (380 mL), the resulting solution was cooled below 0˚C on an ice-salt bath and a solution of $NaIO_4$ (124 g, 0.567 mol) in water (1.05 L) was added dropwise under intense mechanical stirring. Ethanol (190 mL) was added, the stirring was continued on the cooling bath, monitoring the end of the reaction by TLC (I, $R_{f\,2}$= 0,40, $R_{f\,4}$= 0,64). $NaIO_3$ was filtered off, washed on filter with ethanol (190 mL) and then with chloroform (3×140 mL). The ethanol solutions were concentrated to dryness, the concentrate was dissolved in chloroform used in washings of sodium iodate precipitate, washed with brine (140 mL), dried (Na_2SO_4) and half of the solution was used in the next step for the oxidation of dialdehyde **4** to diacid **6**.

The crude aldehyde solution was concentrated under reduced pressure, the concentrate was dissolved in acetone (500 mL), the solution was cooled on an ice-salt bath and then 2.44 M Jones solution (222.5 mL, 0.543 mol) were added dropwise. TLC (I, $R_{f\,4}$= 0.64, $R_{f\,6}$ = 0.11; the diacid was hardly visualized with iodine and H_2SO_4 reagent) confirmed the consumption of the dialdehyde after 3 h and then isopropanol (30 mL) was added. After stirring for 1 h, the reaction mixture was filtered off, washed with acetone (2×300 mL) and the filtrates were concentrated under reduced pressure. The concentrate was extracted with ethyl ether (3×300 mL). The salts were dissolved in brine and extracted with ethyl ether (3×300 mL). The unified ether solutions were extracted with a solution of KOH (51.45 g) in water (400 mL) in three portions and concentrated to dryness, resulting 3.5 g of neutral secondary compounds. The alkaline solutions were acidified to pH 5.5 with con. HCl, concentrated under reduced pressure, the concentrate was extracted with ethyl ether (4×300 mL), the ether solution dried (Na_2SO_4) and concentrated to dryness, resulting 51 g of crude diacid **6**. By crystallization from ethyl acetate, 41.97 g (78 %) of crystallized compound **6** were obtained, mp 218.0-221.0˚C, ^{1}H-NMR (DMSO-d_6, δ ppm, *J* Hz): 2.75 (dd, 2H, H-1, H-3, 5.9, 8.8), 2.66 (m, 2H, H-3a, H-6a), 1.80 (q, 1H, H-2, 12.5), 1.66 (m, 3H, H-2, 2H-4), 1.57 (dq, 1H, H-5, 2.8, 5.6), 1.21 (m, 1H, H-5), 1.05 (m, 2H, H-4, H-6), ^{13}C-NMR (DMSO-d_6, δ ppm): 173.63 (COO), 46.10 (C-1, C-3), 44.01 (C-3a, C-6a), 30.05 (C-4, C-6), 28.04 (C-2), 26.89 (C-5), M = 198.21, M-1 =197.2.

The diacid **5** was obtained in 72.5 % yield by the same procedure, starting from **1**.

*3. Synthesis of diester **9**.*

Diacid **6** (22.8 g, 0.115 mol) was added to a solution of TsOH (2 g) in methanol (250 mL) and stirred overnight at rt, monitoring the end of the reaction by TLC (II, $R_{f\,6}$ = 0.51, $R_{f\,9}$ = 0.78). $NaHCO_3$ (3 g) was added, the solution was concentrated under reduced pressure, the concentrate was taken in ethyl acetate (150 mL), the solution was washed with sat. soln. $NaHCO_3$ (50 mL), brine (30 mL), dried (Na_2SO_4), concentrated, coevaporated with benzene, resulting 25 g of crystallized crude diester. By crystallization from ethyl acetate-hexane, we obtained 23.3 g (91.1 %) of pure product, mp 71.0-73.1 ˚C, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.68 (s, 6H, CH_3O), 2,80 (m, 4H, H-1, H-3, H-3a, H-6a), 2.14 (q, 1H, H-2, 12.8), 1.91 (m, 1H, H-2), 1.72 (m, 2H, H-4, H-6), 1.66 (tt, 1H, H-5, 2.3, 5.8), 1.27 (m, 1H, H-5), 1.11 (m, 2H, H-4, H-6), ^{13}C-NMR ($CDCl_3$, δ ppm): 173.72 (COO), 51.29 (CH_3O), 46.55 (C-1, C-3), 44.51 (C-3a, C-6a), 30.24 (C-4, C-6), 27.78 (C-2), 27.10 (C-5).

*4. Synthesis of saturated anhydride **8***

The diacid **6** (7.45 g, 37.6 mmol) was added to acetic anhydride (150 mL) and stirred at 80-90˚C for 9 h, monitoring the end of the reaction by TLC (II, $R_{f\,6}$ = 0.51, $R_{f\,8}$ = 0.75). The reaction mixture was concentrated under reduced pressure, co-evaporated with toluene, the concentrate was taken in toluene (200 mL), the solution was washed with 10 % $KHCO_3$ (2×50 mL), brine (30 mL), dried (Na_2SO_4) and concentrated, resulting 6.77 g (quantitative) of anhydride, **8**. A sample was crystallized from toluene-hexane, mp 155.8-157.3˚C, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.24 (m, 2H, H-1, H-3), 2.97 (m, 2H, H-3a, H-6a), 2.34 (d, 1H, H-2, 12.6), 2.00 (dt, 1H, H-2, 4.0, 12.6), 1.78 (m, 2H, H-4, H-6), 1.67 (m, 2H, H-5), 1.49 (m, 2H, H-4, H-6), ^{13}C-NMR ($CDCl_3$, δ ppm): 168.86 (COO), 46.62 (C-1, C-3), 46.06 (C-3a, C-6a), 34.05 (C-2), 27.66 (C-4, C-6), 27.45 (C-5).

*5. Synthesis of un-saturated anhydride **7***

The un-saturated diacid **5** (7.77 g, 39.6 mmol) was stirred in acetic anhydride (150 mL) at 70-80˚C as in example 4. TLC (II, $R_{f\,5}$ = 0.39, $R_{f\,7}$ = 0.73). After similar work-up, 5.74 g (81.3 %) of compound **7** were otained, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 5.78 (dq, 1H, H-6, 2.2, 5.8), 5.64 (dq, 1H, H-5, 2.2, 5.8), 3.43 (m, 1H, H-6a), 3.46 (ddt, 1H, H-1, 1.1, 4.0, 7.3), 3.31 (dt, 1H, H-3, 3.7, 7.1), 3.15 (m, 1H, H-3a), 2.59 (m, 1H, H-4), 2.33 (m, 2H, H-2, H-4), 1.97 (dt, 1H, H-2, 4.0, 12.6), ^{13}C-NMR ($CDCl_3$, δ ppm): 168.45, 168.19 (COO), 133.21 (C-6), 128.33 (C-5), 52.66 (C-6a), 46.96, 46.90 (C-1, C-3), 42.35 (C-3a), 33.25 (C-4), 32.21 (C-2).

*6. Synthesis of β-ketophosphonates **12** and **13***

To a solution of DMPh (14.5 g, 0.113 mol) in THF (300 mL), cooled below -65˚C, in inert anh. atmosphere (Ar), a solution of 1.7 M *n*-BuLi in hexanes (73 mL) was added dropwise, stirred for 15 min. and then a solution of diester **9** (12.5 g, 55.2 mmol) in THF (85 mL) was added dropwise during 30 min. The temperature of the reaction mixture was slowly increased to -30˚C in 2.5 h, monitoring the end of the reaction by TLC (II, $R_{f\,9}$ = 0,75, $R_{f\,13}$ = 0.40, $R_{f\,12}$ = 0.09; III, $R_{f\,13}$ = 0.51, $R_{f\,12}$ = 0.11). Acid acetic (15 mL) was added to neutralize the base, stirring was continued for 5 min. and the solvents were distilled under reduced pressure. The residue was taken in water (50 mL) and ethyl acetate (150 mL), phases were separated (aqueous phase extracted with 3×150 mL ethyl acetate), organic phases washed with 30% $NaHPO_4$ soln. (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated to dryness. The crude product (24.5 g) was purified by LPC (eluent: ethyl acetate-hexane, 1:1), resulting two pure fractions of β-ketophosphonates **12** and **13**:

-5.91 g (33.5 %) mono β-ketophosphonate **13**, as an oil, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.80 (d, 3H, OC$\underline{H}_3$, J_{HP} =11.3), 3.79 (d, 3H, OC$\underline{H}_3$, J_{HP} =11.3), 3.67 (s, 3H, OCH_3), 3.29 (dd, 1H, C$\underline{H}_2$P, J_{HP} = 22.7, J_{gem} = 14.0), 3.20 (m, 1H, H-3), 2.99 (dd, 1H, C$\underline{H}_2$P, J_{HP} = 22.7, J_{gem} = 14.0), 2.90-2.78 (m, 2H, H1, H-3a), 1.83-1.61 (m, 4H, H-2, H-4, H-6, H-6a), 1.35-0.85 (m, 5H, H-2, H-4, 2H-5, H-6), ^{13}C-NMR ($CDCl_3$, δ ppm): 201.36 (d, $\underline{C}$O, 6.2), 173.69 ($\underline{C}OOCH_3$), 55.16 (C-3), 53.21 (d, PO$\underline{C}H_3$, J_{CP} = 6.5), 52.97 (d, PO$\underline{C}H_3$, J_{CP} = 6.5), 51.36 (COO$\underline{C}H_3$), 46.28 (C-1), 44.96 (C-6a), 44.07 (C-3a), 40.55 (d, $\underline{C}H_2$P, J_{CP} = 129.3), 29.97 (C-6 or C-4), 29.78 (C-4 or C-6), 27.30 (C-5), 26.63 (C-2).

-7.27 g (32.1 %) bis β-ketophosphonate **12**, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.80 (d, 6H, POC$\underline{H}_3$, J_{HP} =11.3), 3.79 (d, 6H, OC$\underline{H}_3$, J_{HP} =11.3), 3.30 (d, 2H, C$\underline{H}_2$P, J_{HP} = 22.8), 3.29 (d, 1H, C$\underline{H}_2$P, J_{HP} = 22.7), 3.10-2.80

(m, 4H, H-1, H-3, H-3a, H-6a), 2.15-1.90 (m, 2H, 2H-2), 1.75-1.63 (m, 2H, H-4, H-6), 1.50-1.30 (m, 2H, H-5), 1.10-0.85 (m, 2H, H-4, H-6), ^{13}C-NMR ($CDCl_3$, δ ppm): 201.18 (d, CO, J_{CP} = 6.7), 54.76 (C-1, C-3), 53.18 (d, POCH$_3$, J_{CP} = 6.5), 53.00 (d, POCH$_3$, J_{CP} = 6.5), 44.45 (C-3a, C-6a), 40.59 (d, CH$_2$P, J_{CP} = 128.4), 29.47 (C-4, C-6), 27.46 (C-5), 25.57 (C-2). The fraction with the mixture of the phosphonates **12** and **13** (6.6 g) was repurified, resulting 2.46 g of mono β-ketophosphonate **13** (total yield, 47.4%) and 2.25 g of bis β-ketophosphonate **12** (total yield, 42.0%).

*7. Synthesis of β-ketophosphonate **11***

A solution of 1.7 M *n*-BuLi in hexanes (48.1 mL, 81.7 mmol) was added dropwise under mechanical stirring to a solution of DMPh 97 % (9.95 g, 8.6 mL, 77.77 mmol) in anh. THF (200 mL), which had been cooled to < -70°C in an inert anh. atmosphere (Ar). After 40 min of stirring, a solution of saturated anhydride **8** (6.37 g, 35.35 mmol) in THF (40 mL) was added dropwise. Stirring was continued for 100 min at a temperature below -60°C, then the temperature was allowed to increase to -35°C, monitoring the end of the reaction by TLC (I, $R_{f\ 8}$ = 0.77, $R_{f\ 11}$ =0.13). TLC showed the end of the reaction after 30 min. Acetic acid was added, stirred for 5 min. and the solvents were distilled under pressure. The residue was taken in water (100mL) and ethyl acetate (150 mL), phases were separated (aqueous phase extracted with 3×150 mL ethyl acetate), organic phases were extracted with 10 % $KHCO_3$ (3×75 mL), brine (25 mL), dried and concentrated. The aqueous phases were acidified to pH 3, extracted with ethyl acetate (100 mL ×, control TLC), organic phases washed with brine (20 mL), dried ($MgSO_4$) and concentrated to dryness. The residue was taken in warm toluene and the β-ketophosphonate **11** crystallized at rt, resulting 3.70 g (34.4 %), mp 148-150°C, IR (KBr): 3250-2500 large band (with peaks at: 2967s, 2935s, 2865s), 1724vs ($\nu_{C=O}$), 1706 (ν_{COOH}), 1393m, 1240vs ($\nu_{P=O}$), 1207s, 1165s, 1106m, 1036vs (ν_{P-O-C}), 1024m, 895m, 860s, 832vs (ν_{P-O-C}), 674m, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 3.66 (d, 3H, OCH$_3$, J_{HP} = 11.1), 3.65 (d, 3H, OCH$_3$, J_{HP} = 11.1), 3.50 (dd, 1H, CH$_2$P, J_{HP} = 22.0, J_{gem} = 14.3), 3.12 (dd, 1H, CH$_2$P, J_{HP} = 22.0, J_{gem} = 14.3), 3.06 (t, 1H, H-3, 6.3), 2.86 (qv, 1H, H-3a, 8.5), 2.77 (m, 1H, H-1, 5.9, 9.1), 2.70 (m, 1H, H-6a, 5.9, 9.1, 12.0), 1.81 (q, 1H, H-2, 12.6), 1.72-1.59 (m, 2H, H-4, H-6), 1.59-1.49 (m, 2H, H-2, H-5), 1.18 (dq, 1H, H-5, 5.8, 11.8), 1.00 (m, 1H, H-6, 5.9, 8.3, 12.0), 0.78 (m, 1H, H-4, 5.9, 9.1, 12.0), ^{13}C-NMR ($CDCl_3$, δ ppm): 202.26 (CO), 174.41 (COOH), 54.52, 54.49 (C-3), 52.62 (d, OCH$_3$, J_{CP} = 5.8), 52.51 (d, OCH$_3$, J_{CP} = 5.8), 45.81 (C-1), 44.11 (C-6a), 43.55 (C-3a), 40,05 (d, CH$_2$P, $J_{C\ P}$ = 129) in DMSO, 29.77 (C-6), 29.32 (C-4), 26.92 (C-5), 26.59 (C-2). M = 304.27, M-1 = 303.22, fragment: 269. By LPC purification of the mother liquors, another 5.35 g of the β-ketophosphonate **11** were obtained (total yield, 84.1 %).

*8. Esterification of β-ketophosphonate **11** to β-ketophosphonate **13** with diazomethane*

20 mL Of a solution of diazomethane in ethyl ether were added to a solution of 100 mg β-ketophosphonate **11** in 5 mL chloroform, and stirred at rt (the yellow color to persist at the end of the reaction), monitoring the end of the reaction by TLC (II, $R_{f\ 11}$ = 0.29, $R_{f\ 13}$ = 0.40). The solvents were distilled and the product, though almost pure, was purified by LPC, resulting 95 mg (92%) β-ketopphosphonate **13**, with NMR identical to that of β-ketopphosphonate **13**.

*9. Synthesis of β-ketophosphonate **10***

In the reaction conditions presented at the example 7, starting from 3.56 g (20 mmol) **7** in 25 mL THF, 5.6 g DMPh (44 mmol) in 110 mL THF, 27 mL 1.7 M *n*-BuLi solution in hexanes, TLC (II, $R_{f\ 7}$ = 0.71, R_{f} **10** =0.11), 4.44 g (73.5 %) of pure β-ketophosphonate **10** were obtained, mp 113-114°C (acetone), IR (KBr): 3250-2300 large band (with peaks at 2954s, 2911s), 1715vs ($\nu_{C=O}$), 1705 (ν_{COOH}), 1375m, 1289vs ($\nu_{P=O}$), 1210s, 1201s, 1053vs (ν_{P-O-C}), 1032vs, 910m, 866vs, 807s (ν_{P-O-C}), ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 12.16 (COOH), 5.69 (dq, 1H, H-6, 2.1, 5.8), 5.37 (dq, 0.5H, H-5, 2.3, 5.8), 5.30 (dq, 0.5H, H-5, 2.3, 5.8), 3.67 (d, 3H, OCH$_3$, J_{HP} = 11.2), 3.65 (d, 3H, OCH$_3$, J_{HP} = 11.2), 3.53 (dd, 0.5H, CH$_2$P, J_{HP} = 22.1, J_{gem} = 14.4), 3.51 (dd, 0.5H, CH$_2$P, J_{HP} = 22.1, J_{gem} = 14.4), 3.48 (m, 1H, H-6a), 3.24 (dd, 0.5H, CH$_2$P, J_{HP} = 21.8, J_{gem} = 14.5), 3.21 (dd, 0.5H, CH$_2$P, J_{HP} = 21.8, J_{gem} = 14.5), 3.13 (m, 1H, H-3, 5.4, 8.7), 3.03 (dq, 1H, H-3a, 4.4, 8.4), 2.85 (m, 1H, H-1), 2.41 (m, 1H, H-4), 1.98 (m, 1H, H-4), 1.78-1.50 (m, 2H, H-2), ^{13}C-NMR ($CDCl_3$, δ ppm): 202.79, 201.75 (CO), 174.49, 173.97 (COOH), 132.57, 132.42 (C-6), 129.32, 129.01 (C-5), 55.80, 55.76, 55.72 (C-6a), 52.69 (d, OCH$_3$, J_{CP} = 6.8), 52.57 (d, OCH$_3$, J_{CP} = 6.0), 51.69, 51.42 (C-3), 47.34, 46.89 (C-1), 41.04 (C-3a), 40.87 (d, CH$_2$P, $J_{C\ P}$ = 128.8) in DMSO, 36.24, 35.85 (C-4), 26.84 (C-2).

*10. Synthesis of prostaglandin analogue **16***

a) 70 % $HClO_4$ (0.25 mL) was added to a solution of prostaglandin intermediate **14** (2.63 g, 5 mmol) in acetone (130 mL) and the solution was stirred overnight at rt, monitoring the end of the reaction by TLC (IV, $R_{f\ 14}$ = 0.46, $R_{f\ 15}$ = 0.40). $HClO_4$ was neutralized with $KHCO_3$ solid, the acetone was distilled under reduced pressure, the residue was taken in benzene (100 mL), the benzene solution was washed with 10 % $KHCO_3$ soln. (20 mL), brine (20 mL), dried ($MgSO_4$), concentrated, and co-evaporated with anh. benzene to about 20 mL. The solution was used as such in the next reaction.

b) A solution of β-ketophosphonate **13** (1.59 g, 5 mmol) in THF (20 mL) was added dropwise in inert anh. atmosphere (Ar) to a suspension of NaH (hexane washed) (123 mg, 5.1 mmol) in THF (20 mL), cooled to an ice bath, and stirred for 30 min. Then the solution of aldehyde **15** in benzene was added dropwise and stirred for 5 h, monitoring the end of the reaction by TLC (II, $R_{f\ 15}$ = 0.40, $R_{f\ 16}$ = 0.25, $R_{f\ phosphonate\ 13}$ = 0.51). Acetic acid (1.5 mL) was added, the solvents were distilled under reduced pressure and the residue was purified by LPC (eluent, ethyl acetate-hexane, 1:1), resulting 2.39 g (71.3 %) prostaglandin compound **16**, as an oil, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.10-8.06 (2m, 2H, H-*o*), 7.93-7.86 (2m, H-*o*), 7.60 (tt, 1H, H-*p*, 7.4, 1.3), 7.51 (tt, 1H, H-*p*, 7.5, 1.4), 7.46 (tl, 2H, H-*m*,7.3), 7.33 (tl, 2H, H-*m*, 7.4), 6.92 (dd, 0.5H, H-13, 15.8, 2.1), 6.89 (dd, 0.5H, H-13, 15.8, 2.1), 5.52-5.35 (m, 4H, H-5, H-6, H-9, H-11), 3.68 (s, 3H, CH_3O-BC), 3.61 (s, 3H, CH_3O-C$_1$), 3.20-2.64 (m, 6H), 2.42-2.00 (m, 2H), 1.42-1.92 (m, 2H), 1.30-0.80 (m, 2H), ^{13}C-NMR ($CDCl_3$, δ ppm): 199.45, 199.32 (CO), 174.06, 173.92 (COO), 165.97, 165.70 (COO-Ph), 145.10 (C-13), 133.19, 133.09 (2C-*p*), 131.52, 131.45 (d, C-14), 130.69 (C-5 or C-6), 130.17, 129.66 (Cq, Bz), 129.56, 129.52 (C-*o*), 128.45, 128.27 (CH, C-*m*), 127.06 (C-6 or C-5), 78.19, 78.14 (d, C-11), 75.21 (C-9), 53.42, 53.28 (d, C-12), 52.33, 52.25 (d, C-1'), 51.42 (2CH_3O), 48.63, 48.53 (CH, C-), 46.39 (2C, C-1, C-3), 45.19, 44.80 (CH, C-), 39.20, 39.13 (C-10), 33.25 (C-2), 30.05, 29.82 (C-4', C-6'), 27.28 (C-2'), 26.63 (C-5', C-4), 25.55, 25.47 (CH_2, C-), 24.56 (CH_2, C-).

A patent request [12] with the synthesis of β-ketophosphonates having a functionalized hexahydro-and octahydropentalene fragment linked to the ketone group was submitted to OSIM, Romania.

Conclusions

β-Ketophosphonates, with the keto group linked to the bicyclo[3.3.0]oct(a)ene fragment, were synthesized. Diacids **5** and **6** were transformed into internal anhydrides **7** and **8**, which were reacted with lithium salt of dimethyl methanephosphonate to obtain the acid phosphonates **10** and **11**. The saturated di-acid was esterified to the dimethyl ester **9** which was reacted with lithium salt of dimethyl methanephosphonate to obtain the mono β-ketophosphonates **13** and bis β-ketophosphonates **12**. The acid β-ketophosphonate **11** was esterified with diazomethane to the ester β-ketophosphonate **13**, and the synthesis of **13** from anhydride **8** and from diester **9**, confirmed the structure of both compounds. A *E*-HEW selective olefination of the prostaglandin aldehyde **15** having an α-side chain, with the β-ketophosphonate **13** was realized to give the 15-keto prostaglandin analogue **16** in good yield. The following step, that is, the selective reduction of the 15-ketone group with aluminium diisobornyloxyisopropoxyde, gave no 15-allylic alcohol. This shows that the bicyclo[3.3.0]octane skeleton, linked to the C_{15} carbon atom, is bulky enough to block the access of the also bulky reducing reagent and this fact predicts that the access of the prostaglandin receptor(s) to the 15α-OH active form of the prostaglandin will be diminished. The compounds, all obtained in good yields, were characterized by elemental analysis, (a few by MS), IR and high resolution ^{1}H- and ^{13}C-NMR spectroscopy.

Conflicts of interest

There are no conflicts to declare.

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