ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
https://www.icf.ro/rrch/

Rev. Roum. Chim.,
2022, *67*(1-2), 71–77
DOI: 10.33224/rrch.2022.67.1-2.05

Dedicated to the memory of
Dr. Emilian GEORGESCU (1946-2020)

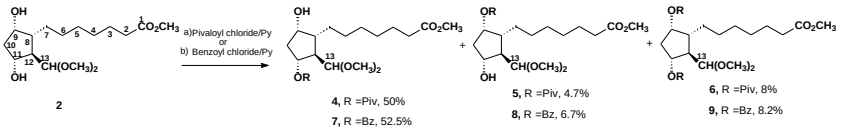
A SELECTIVE PROTECTION BETWEEN 9- AND 11-HYDROXYL OF A PROSTAGLANDIN INTERMEDIATE WITH α-CHAIN AND DIMETHYL ACETAL, FOR BUILDING THE ω-SIDE CHAIN

Constantin I. TĂNASE,[a] Constantin DRĂGHICI,[b] Miron T. CAPROIU[B] and Lucia PINTILIE[a,*]

[a] National Institute for Chemical-Pharmaceutical Research and Development-ICCF, 112 Vitan Av., 031299, Bucharest-3, Roumania, cvtanase@gmail.com (CIT), lucia.pintilie@gmail.com (LP)
[b] "Costin D. Nenitzescu" Institute of Organic and Supramolecular Chemistry, 202B Splaiul Independenței, 060023, Bucharest, Roumania, cst_drag@yahoo.com (CD), dorucaproiu@gmail.com (MTC)

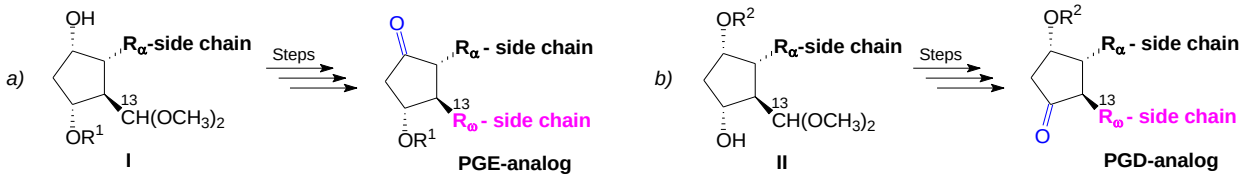
Received August 4, 2021

Hydrogenation of the 5,6-double bond of the 11-THP protected 13-dimethylacetal, without careful neutralization of the acidity of the Pd/C catalyst, conducted to the removal of the THP group with the consequence of no possibility to use selectively the 9- or 11-hydroxyl groups in the next step of prostaglandin synthesis. The selective protection of the 11-hydroxyl group of the hydrogenated compound **2** and good LPC was realized in 50% as pivalate and 52.4% as benzoate; the compound is key intermediate for synthesis of PGE_1 analogs. The other pure separated compounds are also key intermediates for PGF_1 analogs (9,11-bis-esters, **6** and **9**) or PGD_1 (9-esters, **5** and **8**).



INTRODUCTION

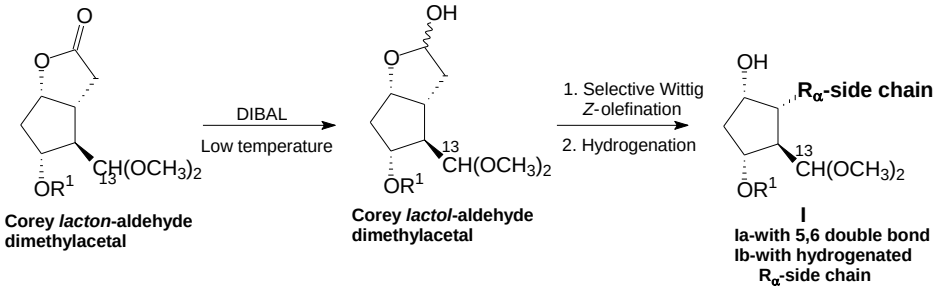
In the prostaglandin (PG) synthesis, it is important to have selective protection between 9- and 11-hydroxyl of the PG intermediates to open their use to build PGE (Scheme 1, *a)*) and PGD analogs (Scheme 1, *b)*), without impurities of PGD in PGE or vice-versa, PGE in PGD.



Scheme 1 – The obtaining of the PGE-analogs from the intermediate **I** (*a)* and of the PGD-analogs from the intermediate **II** (*b)*.

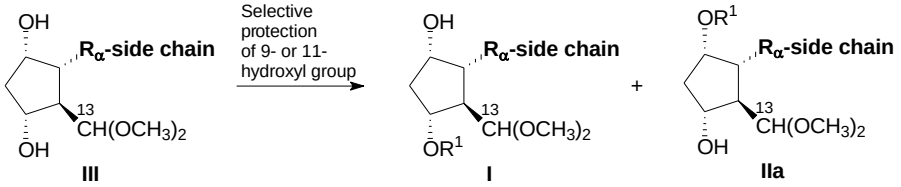
The most used procedure is to build pure the intermediates **I** and **II**, by the protection of the hydroxyls in previous steps, or by (usually) changing R^1 and R^2or vice versa. The easier access to the intermediates **I** is depicted in Scheme 2:

* Corresponding author: lucia.pintilie@gmail.com



Scheme 2 – Synthesis of the intermediates **I** (**Ia** and **Ib**) from the Corey-lacton aldehyde dimethylacetal.

First step: Reduction of the lactone group to lactol with DIBAL; Step 2: Selective Wittig *Z*-olefination for building the α-side chain of the PG_2 analogs to key intermediates **Ia**. Step 3: Catalytic hydrogenation of 5,6-double bond for building the α-side chain of the PG_1 analogs to key intermediates **Ib**.



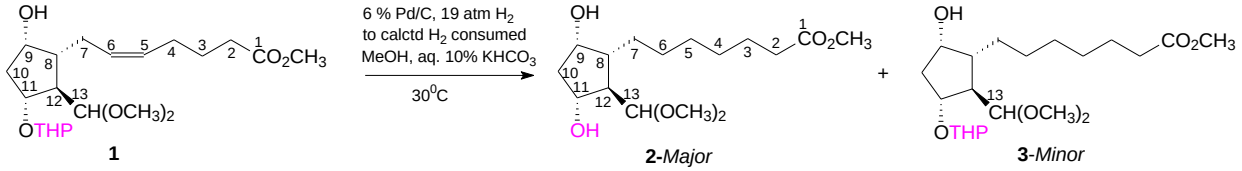
Scheme 3 – Selective protection of the 9- and 11-hydroxyl groups of the compound **III**.

The Corey-lacton-aldehyde is unambiguously protected at the 11-hydroxyl (PG-numbering), or the previously Corey lacton-alcohol is first protected, followed then by oxidation to the aldehyde and finally the aldehyde is protected as dimethyl acetal.[1] The reduction of the lactone group is usually performed by DIBAL reduction at low temperature. In the next step, the α-side chain is introduced by a *Z*-selective Wittig olefination, resulting the intermediates **Ia** for obtaining the series of PG_2 analogs. The catalytic hydrogenation of the 5,6-double bond leads to the purest intermediates **Ib** to obtain the series of PG_1 analogs. Of course, in the literature, selective catalytic hydrogenation of only 5,6-double bond of the prostaglandin compounds are mentioned,[2-4] but the small impurities resulted by concomitant hydrogenation of only 13,14-double bond or both 5,6 and 13,14 double bonds must be removed by low pressure chromatography (LPC).

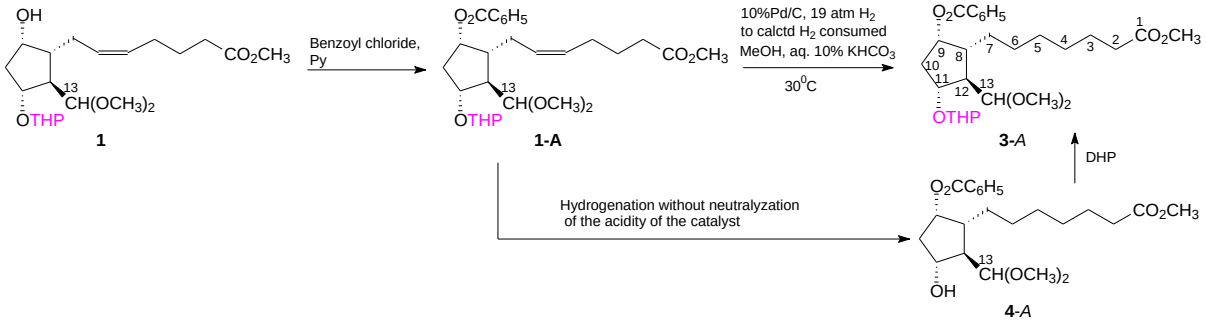
The selective protection of the 9- or 11-hydroxyl in the compound **III** (Scheme 3) is difficult, and in this paper, we describe our effort to obtain pure 9- or 11-hydroxyl compounds protected as pivalate or benzoate group.

RESULTS AND DISCUSSION

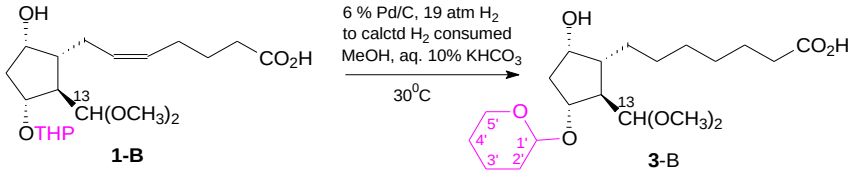
This paper started from an unpleasant event in the catalytic hydrogenation of the THP protected compound **1** (Scheme 4) on 6% Pd/C as catalyst, in methanol as solvent (rt, 19 atm H_2). We neutralized the acidity of the catalyst with 10% $KHCO_3$, we introduced it in the autoclave, and obtained the compound **3** in 90%. NMR showed that the compound contained minor amounts of un-hydrogenated started compound **1**. The crude compound **3** was re-hydrogenated in the same conditions with the same catalyst (previously used), without adding sat. soln. $KHCO_3$, for 3 h at 28˚C. The result was that during hydrogenation (TLC), and similar work-up, the desired THP protected compound **3** was obtained in < 17% yield. The hydrogenated compound **2** remained in the aqueous phase and was extracted with dichloromethane; the compound **2** was obtained in 82% yield. Though the aqueous phase of the first hydrogenation was not extracted with dichloro-methane, it is expected that > 9% of the THP group of the compound **3** was deprotected (Example 1). In conclusion, the acidity of the catalyst must be carefully neutralized previously to be used in hydrogenation of the compounds with labile protected groups, like THP. Side-products in the hydrogenation of the PG intermediates with ω-side chain were identified and characterized in our previous paper [5]. By neutralization of the acidity of the catalyst and hydrogenation of the compound **1** at pressure atmosphere of hydrogen, the yield of compound **3** was near quantitative (Example 2).



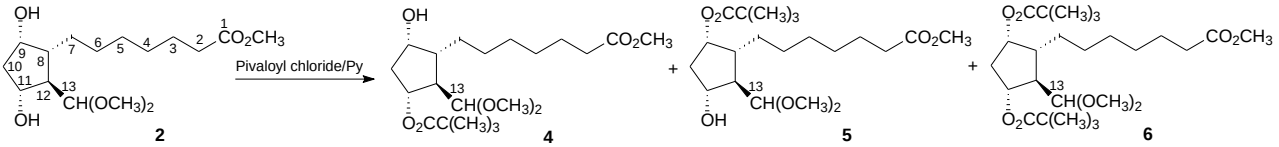
Scheme 4 – Hydrogenation of the compound **1**, *a)* with excess of 10% $KHCO_3$, gave the compound **3** in 90% **3** *b)* with insufficient neutralization of the acidity of the catalyst, the compound **2** (Major) was obtained in 80% and **3** (minor) in <17% (Example 1).



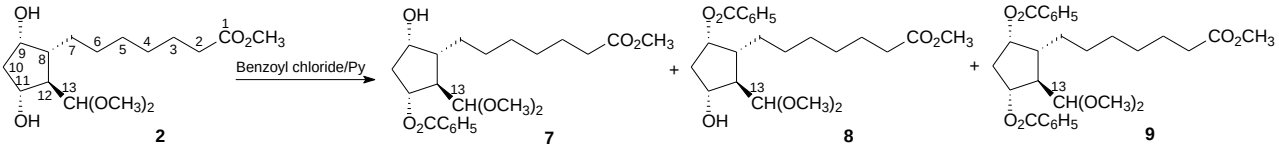
Scheme 5 – The benzoylation of the compound **1** to compound **1-A**, followed by hydrogenation to the compound **3-A**; without neutralization of the acidity of the catalyst, the key intermediate **4-A** for building PGD_1 analogs is directly obtained.



Scheme 6 – The hydrogenation of the compound **1-B** to compound **3-B**.



Scheme 7 – The selective protection of the 11-hydroxyl group of the compound **2** as pivalate (compound **4**) in 50% yield; the side compounds **5** (9-pivalate) and **6** (9,11-bis-pivalate) are formed in 4.7% yield, respectively 8% yield.



Scheme 8 – The selective protection of the 11-hydroxyl group of the compound **2** as benzoate (compound **7**) in 52.5% yield; the side-compounds **8** (9-benzoate) and **9** (9,11-bis-benzoate) are formed in 6.7% yield, respectively 8.2% yield.

To prevent the situation of the deprotection of the THP group of the compound **3**, we firstly protect the 9-hydroxyl group of the compound **1** with benzoate to the compound **1-A** (in quantitative yield) and then we hydrogenate it to the compound **3-A** (Scheme 5). The compound **3-A** was obtained in this variant in 96% yield (on crude product, Example 3). Even if the THP group of the compound **3-A** could be deprotected during hydrogenation to the compound **4-A**, this group could be re-introduced at this stage by etherification with DHP. If the compound **4-A** is

intended to be used for obtaining PGD_1 analogs, the hydrogenation could be performed without neutralization of the catalyst. It is worth mentioning that the key compound **3-A** is stable and used in both direction to PGE_1 analogs or PGD_1 analogs by selective deprotection of 9-benzoate or 11-THP group, followed by oxidation of the free hydroxyl to keto group.

The hydrogenation of the acid compound **1B** was realized in the same good conditions used in the Example 2; the compound **3-B** was obtained in 92% yield (Scheme 6; Example 4), without deprotection of the THP group.

The deprotected compound **2**, obtained in the Example 1, could be used directly for the synthesis of PGF_1 analogs. For obtaining the PGE_1 or PGD_1 analogs, the selective protection of the 11-hydroxyl, in the first case, and 9-hydroxyl, in the second case, is imperious requested to introduce selectively the 9-keto, respectively 11-keto group by oxidation of the free hydroxyls of the corresponding compounds. In this direction we tried to selective protect the 11-hydroxyl group of the compound **2** as pivalate or benzoate, knowing from literature that the least hindered 11-hydroxyl group is more reactive[6] even in the $PGF_{2\alpha}$ which contains three hydroxyl groups in the molecule, 9, 11 and 15; for example, selective monoacylation of only 11-hydroxyl group of $PGF_{2\alpha}$ as pivalate, acetyl, iso-butyryl, valeryl and iso-valeryl is mentioned in a few patents.[7,8] Firstly, we performed the protection of the 11-hydroxyl of the compound **2** as pivalate. Sure, from the reaction the 9-pivalate (**5**) and 9,11-bis-pivalate (**6**) are waited to be obtained also, as described in Scheme 7, but we hoped to succeed in the separation of the compounds by LPC.

The compound **2**, dissolved in pyridine as solvent (at a dilution of 1.43 mL/mmol) and organic base (to neutralize the HCl generated in the reaction), was reacted under stirring with 1.1 equivalents of pivaloyl chloride, added dropwise at -18˚C (cooling on an ice-NaCl bath); the stirring was continued at low temperature, then at rt overnight and the final work-up was usual for esterification with acid chlorides: the reaction mixture poured in crashed ice, sat. soln. $NaHCO_3$ and hexane. The pivalates **4**-**6** were extracted in hexane and very well separated by LPC with the eluent: dichloromethane-acetone (4:1, three purifications), obtaining the 11-pivalate (**4**) in 50% yield. The side-compounds 9-pivalate (**5**) and 9,11-bis-pivalate (**6**) were obtained pure in low yields, 4.7% the first and 8% the second (Example 5). It is worth mentioning that the ratio of the monoprotected pivalates **4**: **5** was good, 10.7:1 in favor of the 11-protected compound **4**. The bis-pivalate compound **6** could be used more advantageously than the compound **2** in the synthesis of PGF_1 analogs because the elimination of the 11-hydroxyl (with the formation of a cyclopentene double bond, in a secondary reaction) during the acid deprotection of the acetal group to aldehyde is prevented.

We used then benzoyl chloride to protect the 11-OH group, instead of pivalate chloride, in the same conditions for esterification of the diol-compound **2** and LPC purification and obtained the 11-benzoate **7** in slightly higher yield (52.5%) then the corresponding pivalate (Scheme 8). 9-Protected benzoate compound **8** was obtained also in a little increased yield (6.7%) than the corresponding pivalate **5** (4.7%). The 9,11-bis- benzoate **9** was obtained in the same yield as 9,11-bis-pivalate (8%). The ratio of the 11-/9-monobenzoates, **7**:**8** (7.8:1) is less than that of the corresponding pivalates, but it is also good. The bis-benzoate could be advantageously used for synthesis of PGF_1 analogs, as 9,11-bis pivalate, with the same observations.

In both reactions, the starting diol-compound **2** remained in the aqueous phases and was extracted with dichloromethane (See experimental), recovering it in ~ 36%, in the reaction with pivalate chloride, and in ~26% in the reaction with benzoyl chloride. The crude recovered diol **2** was re-used in the same reactions, as previously.

In this paper we used dimethyl acetal protection of the aldehyde, but it can be protected as cyclic acetals or thioacetals which we obtained previously crystallized at the level of Corey aldehyde.[9]

EXPERIMENTAL

The progress of the reactions was monitored by TLC on Merck silica gel 60 or $60F_{254}$ plates eluted with the solvent systems: I, dichloromethane-acetone, 4:1. Spots were developed with DNFH in EtOH-H_3PO_4 or 15% H_2SO_4 in MeOH (heating at 110˚C, 10 min.). IR spectra were recorded on FT-IR Bruker Vertex 70 by ATR and frequencies were expressed in cm^{-1}, with the following abbreviations: w = weak, m = medium, s = strong, v = very, br = broad. ^{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 were done for the correct assignment of NMR signals. The numbering of the atoms in the compounds is presented in Schemes 4, 5, 7 and 8.

The hydrogenation of the compound 1 over 6% Pd/C in methanol and 10% soln. $KHCO_3$ to the compounds 2 and 3

The crude compound **1** (208 g as an oil, containing 519 mmol, 87.5%) was dissolved in methanol (1 L) and introduced in a 2L autoclave, then 6% Pd/C (28 g) as catalyst and 10% soln. $KHCO_3$ (26 mL) to neutralize the acidity of the catalyst in methanol (250 mL) were added (the vessels were washed with 300 mL methanol). The hydrogenation has been done at rt and 19 atm. H_2 for 2 hrs. (60% from calculated H_2 was consumed). TLC (I, dichloromethane-acetone, 4:1, $R_{f\ 1}$ = 0.58, R_{f3} = 0.60) did not distinguished clear the end of hydrogenation and another portion of catalyst (28 g) was added; the hydrogenation was continued at 40˚C and 19 atm. H_2 for 2 hrs. until the calculated hydrogen was adsorbed. The pH of the reaction mixture was ~7 at the end of the hydrogenation. The catalyst was filtered off (the autoclave was washed with 3x1L methanol), washed on filter with methanol washings and methanol (1L), the filtrate was concentrated under reduced pressure, water (300 mL) was added and the product was extracted with hexane (1L + 6x0.5 L). The hexane extracts were washed with water (2x500 mL), brine (2 x 250 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to dryness, resulting 187.5 g (468 mmol, 90%, taken into account the same 87.5% purity as starting compound **1**) of crude product (though the pH was 7, in the aqueous phase should remain near 51 mmol, probably as the compound **2**). No deprotection of the THP group was observed. NMR showed that the crude compound contains minor impurity of the un-hydrogenated compound (**1**). The crude product was reintroduced to hydrogenation with the same catalyst (previously used), without adding sat. soln. $KHCO_3$ for 3 h at 28˚C. TLC showed that most of the compound **3** was deprotected to the compound **2** (I, R_{f2} = 0.30). After filtering the catalyst, concentrated to dryness, adding water (300 mL) and hexane (1 L) (the pH of the concentrate with water and hexane was near 3.5?), the hexane extract separated (the extraction with hexane was repeated once more), washed with sat. soln. $NaHCO_3$ (2x200 mL), water (300 mL), brine (200 mL), dried and concentrated to dryness, resulting 28 g (<80 mmol, 17%) of crude compound **3**, methyl 7-((*1R,2R,3R,5S*)-2-(dimethoxymethyl)-5-hydroxy-3-((tetrahydro-2H-pyran-2-yl)oxy)cyclopentyl) heptanoate, as an oil. The water phase was saturated with sodium sulfate, extracted with toluene (2x500 mL, 2x250 mL), organic phases washed with previous aqueous washing solutions, dried (Na_2SO_4), filtered and concentrated under reduced pressure to dryness, resulting 122.4 g (384 mmol, 82%) of almost pure compound **2**, methyl 7-((*1R,2R,3R,5S*)-2-(dimethoxymethyl)-3,5-dihydroxycyclopentyl)heptanoate, as an oil, ^{1}H-NMR-300 MHz (DMSO-d_6, δ ppm, *J* Hz): 3.92-3.90 (m, 2H, H-9, H-11), 4.18 (d, 1H, H-13, 5.1), 3.57 (s, 3H, CH_3OOC), 3.28, 3.27 (2s, 6H, OMe), 2.28 (t, 2H, H-2, 7.4), 2.25 (m, 1H, H-10), 2.10-1.75 (m, 3H, H-10, H-12, H-8), 1.60-1.20 (m, 10H, 2H-3, 2H-4, 2H-5, 2H-6, 2H-7), ^{13}C-NMR-75 MHz (DMSO-d_6, δ ppm): 173.46 (C-1), 106.96 (C-13), 72.30, 71.55 (C-9, C-11), 55.85 (CH_3OO), 54.78, 54.15 (2C, CH_3O-acetal), 51.19 (C-12), 45.12 (C-8), 42.85 (C-10), 33.35 (C-2), 29.12 (C-5), 28.57 (C-4), 28.51 (C-6), 27.40 (C-7), 24.52 (C-3).

The hydrogenation of the compound 1 over 6% Pd/C in methanol in the presence of excess 10% soln. $KHCO_3$ to the compound 3

The crude compound **1** (10.3 g, ~25.7 mmol) in methanol (500 mL) was hydrogenated at 19 atm. H_2 at rt and in the presence of 6% Pd/C catalyst (4 g) and 10% soln. $KHCO_3$ (15 mL) (the pH of the reaction mixture, stirred without H_2 for 15 min. was ~7). After work-up as previously described, 10.23 g of the compound **3**, methyl 7-((*1R,2R,3R,5S*)-2-(dimethoxymethyl)-5-hydroxy-3-((tetrahydro-2H-pyran-2-yl) oxy)cyclopentyl)heptanoate, was obtained as an oil. A fraction was purified by LPC and analyzed by: IR: 3424 large band, 2932vs, 2861s, 1717vs, 1452m, 1358m, 1163s, 1127s, 1070s, 1022s, 870m, ^{1}H-NMR-500 MHz ($CDCl_3$, δ ppm, *J* Hz): 5.07 (m, 1H, H-11), 4.69, 4.57 (2 brt, 1H, H-1'), 4.34, 4.21 (2 d, 1H, H-13, 4.1 and 4.7), 4.16 (m, 1H, H-9), 3.92, 3.80 (2m, 1H, H-5'), 3.46 (m, 1H, H-5'), 3.48, 3.43 (2s, 6H, OMe), 3.41 (s, 3H. CH_3OOC), 2.32 (t, 2H, H-2, 7.4), 2.14 (dt, 1H, H-12, 4.6, 8.9), 2.03 (ddd, 1H, H-10, 4.5, 7.4, 12.9), 1.97-1.22 (m, 18, H-8, H-10, 2H-2', 2H-3', 2H-4', 2H-3, 2H-4, 2H-5, 2H-6, 2H-7), ^{13}C-NMR-125 MHz ($CDCl_3$, δ ppm): 178.75, 178.10 (C-1), 107.32 (C-13), 97.97 (C-1'), 77.79, 77.11m (C-9), 75.87 (C-11), 62.62m, 62.27 (C-5' THP), 55.95, 54.98 (C-12), 55.48, 54.53 (OCH_3-acetal), 50.81 ($\underline{C}H_3OOC$), 44.66m, 44.36 (C-8), 39.80, 38.99 (CH_2, C-10), 33.84, 33.78 (C-2), 39.80, 39.03 (CH_2), 31.05, 30.50 (CH_2), 29.46, 29.30 (C-5), 28.95m, 28.82 (CH_2), 27.66, 27.54 (C-7), 25.55 (CH_2, C-4'), 24.67 (C-3), 19.60, 19.32m (C-3'). A THP group introduces (due to linking of oxygen (of hydroxyl) to C-1 of THP group) a new chiral center and the ratio of resulted isomers is, in this particular case, not 1:1; we used "m" next to a signal pertaining to the minor isomer.[5, 11-12]

9-OH Benzoylation of the compound 1 and the hydrogenation of the compound 1-A to 3-A

a) The compound **1** (20.7 g, 59.1 mmol) was dissolved in toluene (150 mL) and pyridine (25 mL), the solution was cooled to an ice-water bath, benzoyl chloride (11 mL, 13.32 g, 94.8 mmol) was added dropwise and stirred overnight, monitoring the end of the reaction by TLC (I, $R_{f\ 1}$ = 0.58, $R_{f\ 1\text{-}A}$ = 0.67). The reaction mixture was poured on a stirred mixture of 10% soln. $KHCO_3$ (200 mL) and crashed ice (300 g), stirred for 1 h, the phases were separated, organic phase was washed with 10% soln. $KHCO_3$ (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, concentrated to dryness, co-evaporated twice with toluene to remove the pyridine, resulting in near quantitative yield (30.9 g) the crude compound **1-A**, (*1R,2S,3S,4S*)-3-(dimethoxymethyl)-2-((Z)-7-methoxy-7-oxohept-2-en-1-yl)-4-((tetrahydro-2H-pyran-2-yl)oxy)cyclopentyl benzoate. as an oil, used in the next reaction.

b) The crude compound **1-A** (30.9 g, containing ~ 59.1 mmol) was dissolved in methanol (150 mL), 10% soln. $KHCO_3$ (25 mL) and 6% Pd/C (8.2 g) were added, stirred for 15 min. and hydrogenated at rt with H_2 (5 atm) for 6 h. The catalyst was filtered off, washed with methanol (250 mL) and acetone (200 mL) and the filtrate concentrated to dryness. The concentrate was taken in hexane (500 mL) and water (200 mL), the phases were separated, the organic phase was washed with sat. soln. $NaHCO_3$ (250 mL), water (250 mL) and brine (100 mL) (the aqueous phases were extracted with 500 mL hexane), dried (Na_2SO_4), filtered, concentrated to dryness, co-evaporated with benzene, resulting 26 g (96% on crude product) of compound **3-A**, (*1R,2S,3S,4S*)-3-(dimethoxymethyl)-2-(7-methoxy-7-oxoheptyl)-4-((tetrahydro-2H-pyran-2-yl)oxy)cyclopentyl benzoate, as an oil, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 8.10-8.03 (m, 2H, H-*o*), 7.55 (t, 1H, H-*p*, 7.4), 7.43 (brt, 2H, H-m, 7.4), 5.41 (m, 1H, H-9), 4.74 (dd, 2.5, 4.0) and 4.56 (t, 3.3) for H-1', two dd for H-13 [4.38 (d, 4.3) and 4.27 (d, 4.8)], 4.24 (m, 1H, H-11), 3.46, 3.44 (2s, 6H, OMe), 3.42 (s, 3H, CH_3OOC), 3.40 (m, 2H, H-5'), 2.22 (2t,

2H, H-2, 7.4), 2.42-1.22 (m, 20H, H-8, H-12, 2H-10, 2H-3, 2H-4, 2H-5, 2H-6, 2H-7, 2H-2', 2H-3', 2H-4'), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 174.14 (C-1), 166.16 (PhCO), 132.62 (C-*p*), 130.93 (C-*q*, Ph), 129.64 (C-*o*), 128.15 (C-*m*), 107.30 (C-13), 98.30, 96.50 (C-1'), 78.36, 77.19 (C-9), 76.68 (C-11), 61.97, 61.85m (C-5' THF), 55.91, 54.44 (C-12), 55.54, 53.75 (OCH_3-acetal), 51.30 (CH_3OOC), 44.38, 43.92 (C-8), 39.83, 37.40 (C-10), 33.99 (C-2), 31.11, 30.84 (C-5), 29.35 (C-2'), 29.04, 28.92, 28.85 (C-4, C-6), 27.70, 27.64 (C-7), 25.53, 25.48 (C-4'), 19.26, 19.15m (C-3').

The hydrogenation of the compound 1-B over 6% Pd/C in methanol in the presence of excess 10% soln. $KHCO_3$ to the compound 3-B

The compound **1-B** (29 g, 82 mmol) was dissolved in methanol (0.8 L), a solution of $KHCO_3$ (15 g, 150 mmol) in water (200 mL) and the catalyst (6% Pd/C, 8.5 g) were added and stirred for 15 min, then hydrogenated at rt (19 atm H_2) for 3 h. After filtration of the catalyst and removing methanol by distillation at rotavapor, the aqueous phase was acidified to pH 5.5-6 with NaH_2PO_4 (solid) and extracted with dichloromethane (3x300 mL), the extracts were washed with brine (200 mL), dried (Na_2SO_4), filtered, concentrated to dryness, resulting 26.8 g (92%) of crude compound **3-B**, as an oil, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 5.49 (m, 1H, H-11), 4.69 (m, 1H, H-1'), 4.30 (2d, 1H, H-13, 5.5 and 4.8), 4.16 (m, 1H, H-9), 3.86 (m, 1H, H-5'), 3.51 (m, 1H, H-5'), 3.40, 3.39 (2s, 6H, OCH_3) 2.32 (t, 2H, H-2, 6.7), 1.90÷1.20 (m, 18H, 6THP, 12H (H-3, H-4, H-5, H-6, H-7, H-10)), ^{13}C-NMR ($CDCl_3$, δ ppm): 178.87 (C-1), 107.25 (C-13), 97.03 (C-1'), 96.59 (C-1'), 79.41 (C-9), 79.24 (C-9), 75.13, 74.97 (C-11), 62.54, 61.90 (C-5' THP), 55.73, 55.34 (C-12), 54.43, 53.39 (OCH_3), 46.87, 46.52 (C-8), 41.30, 39.17 (C-10), 33.95 (CH_2-2), 31.11, 30.71 (CH_2-2'), 30.56 (CH_2), 29.86 (CH_2), 29.52 (CH_2), 29.41 (CH_2), 28.99, 28.90 (CH_2), 28.06 (CH_2), 25.36 (CH_2), 24.68 (C-3), 19.51, 19.23 (C-3').

Selective protection of the 11- hydroxyl group of the compound 2 as pivalate

The crude compound **2** (106 g, 333 mmol) was dissolved in pyridine (500 mL) and the solution was cooled to -18˚C on an ice-salt bath. Then 1.1 equivalents 98% pivaloyl chloride (43.2 g, 44.8 mL, 385 mmol) were dropwise added and the mixture stirred overnight on the bath (arriving to rt in 5 hrs.), monitoring the end of the reaction by TLC (I, $R_{f\ 2}$ = 0.30, $R_{f\ 5}$ = 0.62, $R_{f\ 4}$ = 0.72, $R_{f\ 6}$ = 0.81). The reaction mixture was poured under mechanical stirring in crashed ice (900 g), sat. soln. $NaHCO_3$ (1.7 L) and hexane (1.7 L), the stirring was continued until no ice remained, the phases separated, organic phase was washed with sat. soln. $NaHCO_3$ (0.4 L), water (1 L), brine (0.3 L) (the aqueous phases were extracted with 2x700 mL hexane), dried (Na_2SO_4), and concentrated to dryness, resulting 98.7 g of a mixture of pivalates, as an oil. The concentrate was purified by LPC (three purifications) on a silica gel column (eluent: dichloromethane-acetone, 4:1), resulting:

-13.1 g (26.9 mmol, 8%) of pure bis-pivalate **6**, (*1R,3S,4S,5S*)-4-(dimethoxymethyl)-5-(7-methoxy-7-oxoheptyl)cyclopentane-1,3-diyl bis(2,2-dimethylpropanoate), as an oil, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 5.16 (brt, 1H, H-9, 4.5), 5.12 (ddd, 1H, H-11, 1.8, 4.8, 8.4), 4.11 (d, 1H, H-13, 4.1), 3.66 (s, 3H, CH_3OOC), 3.43, 3.38 (2s, 6H, OMe), 2.30 (t, 1H, H-2, 7.5), 2.29-2.22 (m, 2H, H-10), 2.08 (m, 1H, H-12), 1.66-1.22 (m, 10H, 2H-3, 2H-4, 2H-5, 2H-6, 2H-7), 1.21, 1.17 (s, 18H, *t*Bu), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 178.05, 177.78 (COO-Piv), 174.16 (C-1), 106.58 (C-13), 75.59 (C-11), 75.35 (C-9), 55.84, 55.28 (2C, CH_3O-acetal), 52.74 (C-12), 51.49 (CH_3OO), 44.05 (C-8), 39.21 (C-10), 37.42 (Cq-*t*Bu), 33.99 (C-2), 29.45 (C-5), 28.53 (C-4), 28.30 (C-6), 27.58 (C-7), 27.16, 26.86 (6C, $(CH_3)_3C$), 24.81 (C-3).

-6.3 g (15.6 mmol, 4.7%) of 9-pivalate **5**, methyl 7-((*1R,2R,3R,5S*)-2-(dimethoxymethyl)-3-hydroxy-5-(pivaloyloxy)cyclopentyl)heptanoate, as an oil, $[\alpha]_D$ = 40.1˚(1% in THF), ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 5.11 (t, 1H, H-9, 4.8), 4.31 (d, 1H, H-13, 5.3), 4.16 (dt, 1H, H-11, 3.8, 5.0), 3.64 (s, 3H, CH_3OOC), 3.43, 3.39 (2s, 6H, OMe), 2.30 (dd, 1H, H-2, 7.3, 12.1), 2.29-2.22 (m, 2H, H-10), 2.08 (dt, 1H, H-12, 5.3, 11.8), 1.78 (m, 1H, H-8), 1.66-1.22 (m, 10H, 2H-3, 2H-4, 2H-5, 2H-6, 2H-7), 1.18 (s, 9H, *t*Bu), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 177.61 (COO-Piv), 174.18 (C-1), 107.43 (C-13), 75.06 (C-9), 72.95 (C-11), 55.92 (C-12), 54.74, 54.50 (2C, CH_3O-acetal), 51.39 (CH_3OO), 44.36 (C-8), 40.33 (C-10), 38.90 (Cq-*t*Bu), 33.98 (C-2), 29.45 (C-5), 28.99 (C-4), 28.03 (C-6), 27.45 (C-7), 27.08 (3C, $(\underline{C}H_3)_3C$), 24.86 (C-3).

-67.5 g (167.6 mmol, 50%) of pure 11-pivalate **4**, methyl 7-((1R,2R,3R,5S)-2-(dimethoxymethyl)-5-hydroxy-3-(pivaloyloxy)cyclopentyl)heptanoate, as an oil, with the characteristics presented in another paper.[10]

The aqueous phases were extracted with dichloromethane (3x700 mL) (which also extracted the pyridine), dried (Na_2SO_4), co-evaporated with toluene, resulting 39 g (< 122 mmol, ~36%) of crude starting diol **2**, which was used as so in another reaction with pivalate chloride.

Selective protection of the 11- hydroxyl group of the compound 2 as benzoate

The crude compound **2** (68 g, 213 mmol) was dissolved in pyridine (320 mL) and the solution was cooled to -18˚C on an ice-salt bath. Then 1.1 equivalents 98% benzoyl chloride (34.86 g, 28.8 mL, 248 mmol) were dropwise added and the mixture stirred overnight on the bath (arriving to rt in 5 hrs.), monitoring the end of the reaction by TLC (I, $R_{f\ 2}$ = 0.30, $R_{f\ 9}$ = 0.61, $R_{f\ 8}$ = 0.68, $R_{f\ 9}$ = 0.77). After work-up as in example 4): the reaction mixture was poured under mechanical stirring in crashed ice (600 g), sat. soln. $NaHCO_3$ (1.1 L) and hexane (1.1 L), the stirring was continued until no ice remained, the phases separated, organic phase was washed with sat. soln. $NaHCO_3$ (0.26 L), water (0.65 L), brine (0.2 L) (the aqueous phases were extracted with 2x500 mL hexane), dried (Na_2SO_4), and concentrated to dryness, resulting 71 g of a mixture of benzoates, as an oil. The concentrate was purified by LPC (three purifications) on a silica gel column (eluent: dichloromethane-acetone, 4:1), resulting:

-9.2 g (17.5 mmol, 8.2%) dibenzoate **9**, ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.07 (dd, 2H, H^{orto}-Bz-9, 1.4, 8.2), 7.82 (dd, 2H, H^{orto}-Bz-11, 1.4, 8.4), 7.61 (tt, 2H, H^{para}-$Bz^{9,11}$, 1.3, 7.4), 7.50÷7.38 (m, 4H, H^{meta}-$Bz^{9,11}$), 5.51 (m, 1H, H-9 or H-11), 5.41 (dt, 1H, H-9 or H-11, 4.2, 6.7), 4.58 (d, 1H, H-13, 4.0), 3.63 (s, 3H, COOMe), 3.50-3.43 (m, 2H, H-12, H-8), 3.49, 3.44(s, 6H, OMe), 2.50 (dt, 1H, H-10, 3.6, 9.5), 2.32 (t, 2H, H-2, 7.4), 1.80÷1.20 (m, 10H, H^3÷H^7), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 174.26 (C-1), 166.16, 166.01 (COO-Bz), 132.92, 132.78 (C-*p*), 130.69, 130.35 (C_q-Bz), 129.56 (C-*o*), 128.40 (C-*m*), 106.82 (C-13), 78.01 (C-11), 73.84 (C-9), 56.18, 55.63, (2C, CH_3O), 53.92 ($C\underline{H}_3OOC$), 51.47 (C-12), 44.37 (C-8), 39.26 (C-10), 34.05 (C-2), 29.46, 29.39 (C-5), C-4, 28.98 (C-6), 27.89 (C-7), 24.90 (C-3).

-6.1 g (14.4 mmol, 6.7%) of 9-benzoate, **8**, (*1R,2S,3S,4S*)-3-(dimethoxymethyl)-4-hydroxy-2-(7-methoxy-7-oxoheptyl)cyclopentyl benzoate, as an oil, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 8.04 (dd, 2H, H-*o*, 1.6, 8.2), 7.57 (tt, 1H, H-*p*, 1.6, 8.0), 7.45 (t, 2H, H-*m*, 8.0), 5.41 (dt, 1H, H-9, 2.1, 7.1), 4.39 (d, 1H, H-13, 5.4), 4.27 (ddd, 1H, H-11, 4.3, 6.0, 9.9), 3.63 (s, 3H, C$\underline{H}_3$OOC), 3.48, 3.45 (2s, 6H, OC$\underline{H}_3$), 3.39 (dd, 1H, H-12, 6.0, 10.3), 2.41 (ddd, 1H, H-10, 5.3, 8.3, 15.0), 2.32 (m, 1H, H-8), 2.22 (t, 2H, H-2, 7.6), 1.88 (dd, 1H, H-10, 4.5, 15.0), 1.20-1.15 (m, 10H, 2H-3, 2H-4, 2H-5, 2H-6, 2H-7), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 173.97 (C-1), 165.79 (COO-Bz), 132.76 (C-*p*), 130.52 (C_q-Bz), 129.40 (C-*o*), 128.27 (C-*m*), 107.54 (C-13), 75.85 (C-9), 72.71 (C-11), 55.92 (C$\underline{H}_3$OOC), 54.86, 54.63 (2C, CH_3O-acetal), 51.19 (C-12), 44.42 (C-8), 40.29 (C-10), 33.85 (C-2), 29.24 (C-5), 28.79 (C-4), 28.01 (C-6), 27.39 (C-7), 24.71 (C-3).

-47.5 g (112 mmol, 52.5%) of 11-benzoate **7**, (*1R,2R,3R,4S*)-2-(dimethoxymethyl)-4-hydroxy-3-(7-methoxy-7-oxoheptyl)cyclopentyl benzoate, as an oil, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 8.01 (dd, 2H, H-*o*, 1.4, 7.8), 7.55 (tt, 1H, H-*p*, 1.4, 7.8), 7.43 (t, 2H, H-*m*, 7.8), 5.37 (m, 1H, H-11), 4.44 (d, 1H, H-13, 5.5), 4.27 (dt, 1H, H-9, 4.3, 7.5), 3.66 (s, 3H, CH_3OOC), 3.42, 3.38 (2s, 6H, OMe), 3.39 (dd, 1H, H-12, 6.0, 10.3), 2.32 (dd, 1H, H-10, 5.8, 13.3), 2.32 (m, 1H, H-8), 2.22 (t, 2H, H-2, 7.4), 1.88 (m, 1H, H-10), 1.63-1.21 (m, 10H, 2H-3, 2H-4, 2H-5, 2H-6, 2H-7), 3.39 (dd, 1H, H-12, 6.0, 10.3), 2.41 (ddd, 1H, H-10, 5.3, 8.3, 15.0), 2.32 (m, 1H, H-8), 2.22 (t, 2H, H-2, 7.6), 1.88 (dd, 1H, H-10, 4.5, 15.0), 1.20-1.15 (m, 10H, 2H-3, 2H-4, 2H-5, 2H-6, 2H-7), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 174.28 (C-1), 166.03 (COO-Bz), 132.80 (C-*p*), 130.46 (C_q-Bz), 129.69, 129.57 (C-*o*), 128.51, 128.37 (C-*m*), 106.79 (C-13), 78.01 (C-11), 73.84 (C-9), 55.64 (CH_3OO), 55.70, 55.29 (2C, CH_3O-acetal), 51.46 (C-12), 45.92 (C-8), 41.43 (C-10), 34.11 (C-2), 29.70 (C-5), 29.58, 29.13 (C-4, C-6), 27.39 (C-7), 24.94 (C-3).

The aqueous phases were extracted with dichloromethane, as in example 6, co-evaporated with toluene, resulting 20 g (< 66 mmol, < 29%) of crude starting diol **2**, which was used as so in another reaction with benzoyl chloride.

CONCLUSIONS

Hydrogenation of the THP protected compounds **1**, **1-A** and **1-B**, over 6% Pd/C catalyst, with careful neutralization of the acidity of the catalyst, proceeded clean to the desired compounds **3**, **3-A** and **3-B**. The acidity of the catalyst, without careful neutralization, conducted to the deprotection of the THP group (a labile group in the acid conditions); for example, the 11-THP-compound **3** was deprotected in our experiment to the diol **2** in 82%, but without neutralization of the acid catalyst, the THP group could be quantitatively removed during hydrogenation in methanol.

The hydrogenated diol **2** was selectively protected to 11-pivalate **4** in 50% yield and to 11-benzoate compound **7** in 52.4% yield; both compounds are key intermediates for synthesis of PGE_1 analogs. The chromatographic system gave us the possibility to cleanly separate the 11-, 9- and 9,11-bis-pivalates or benzoates. The other pure separated compounds are also key intermediates for PGF_1 analogs (9,11-bis-esters, **6** and **9**) or PGD_1 (9-esters, **5** and **8**).

REFERENCES

1. C. I. Tănase, L. Pintilie and R. E. Tănase, *Int. J. Mol. Sci.*, **2021**, *22*, 1572/1-40p, /doi.org/ 10.3390/ijms22041572.
2. G. K. Koch and J. W. Dalenberg, *Labelled Compds. & Radiopharm.* **1970**, *6*, 395-398.
3. G. W. Holland, J. L. Jernow and P. Rosen, *US Patent 4059576*, Nov 22. 1977.
4. G. Dalmadi, F. Hajdu, I. Hermecz, K. Mozsolits, T. Szabo, Z. Szeverenyi and E. Vajda (CHINOIN), Process for the Preparation of Prostaglandin E_1. *US6069269*, May 30, 2000.
5. C. I. Tănase, F. Cocu, C. Drăghici, A. Hanganu, L. Pintilie, M. Maganu, C. V. A. Munteanu and S. Shova, *New J. Chem*., **2019**, *43*, 7582-7599.
6. C. Tănase, F. Cocu, C. Drăghici, M. T. Căproiu, C. Neguț and D. I. Udeanu, *Rev. Chim. (Bucharest)*, **2016**, *67*, 20-25.
7. M. E. Garst, E. T. Syage, M. B. Roof, D. F. Woodward and M. F, Chan. *US 5476872*/ Dec. 19, 1995.
8. M. E. Garst, E. T. Syage, M. B. Roof, D. F. Woodward and M. F, Chan. *US Ser. Appl. No. 386835*/July 27, 1989.
9. C. Tănase, F. Cocu, M. T. Căproiu and C. Drăghici, *RO Patent 131617*/28.07.2015.
10. C. Tănase, C. Drăghici, M. T. Căproiu, A. Hanganu, L. Pintilie, M. Maganu and E. Gal, *to be submitted*.
11. C. I. Tănase, F. G. Cocu, C. Drăghici and M. T. Căproiu, *Rev. Roum.Chim*., **2008**, *53*, 195–202.
12. C. Tănase and C. Drăghici, *Rev. Roum. Chim*., **2014**, *59*, 845-853.