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Preparation and Chiral HPLC Separation of the Enantiomeric Forms of Natural Prostaglandins

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Abstract: Four enantiomeric forms of natural prostaglandins, *ent*-$PGF_{2\alpha}$ ((−)-**1**), *ent*-PGE_2 ((+)-**2**) *ent*-$PGF_{1\alpha}$ ((−)-**3**), and *ent*-PGE_1 ((+)-**4**) have been synthetized in gram scale by Corey synthesis used in the prostaglandin plants of CHINOIN, Budapest. Chiral HPLC methods have been developed to separate the enantiomeric pairs. Enantiomers of natural prostaglandins can be used as analytical standards to verify the enantiopurity of synthetic prostaglandins, or as biomarkers to study oxidation processes in vivo.

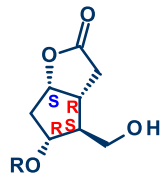
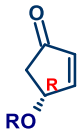
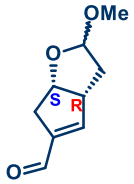
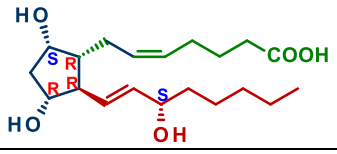
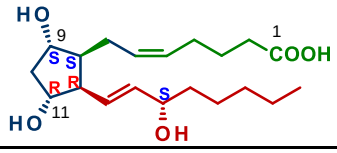
Keywords: preparation; *ent*-$PGF_{2\alpha}$; *ent*-$PGF_{1\alpha}$; *ent*-PGE_2; *ent*-PGE_1; chiral HPLC; enantiomeric separation; mirror images; enantiopurity

1. Introduction

Interest in the field of prostaglandins has been steadily growing since the basic work of Bergström Samuelsson, and Vane [1–3]. Their discoveries revealed the structure, the enzyme-controlled biochemical synthesis from arachidonic acid, and the main physiological effects of prostaglandins as well as their related substances. The biological behavior of prostaglandins, namely the regulation of the functions of all key organs in mammals including humans, has opened promising prospects for their therapeutic use. The request for systematic studies of natural prostaglandins and their synthetic derivatives has forced researchers all over the world to develop economical and scalable syntheses to produce these substances that were previously available only from natural sources [4–6].

The first generally applicable prostaglandin synthesis was a linear one, developed by Corey [7]. The key intermediate in the synthesis is lactone (−)-**5**, commonly referred to as Corey lactone, from which the omega and the alpha side chains of prostaglandins can be constructed [8–10]. The linear approach was followed by convergent syntheses, a more versatile one, a two-component coupling was first applied by Sih [11,12]. Noyori developed the idea of the shortest, highly convergent synthesis, the three-component coupling reaction. Noyori's process provides the prostaglandins or derivatives in a one-pot reaction. The starting material is a chiral cyclopentenone; the omega side chain is introduced by an organo copper-mediated conjugate addition of the optically pure omega side chain. The enolate formed is trapped by the alfa side chain containing alkyl halide [13–15]. Recently, Aggarwal has developed a short, stereocontrolled organocatalytic synthesis starting with the double aldol reaction of succinaldehyde in the presence of a chiral auxiliary. The key intermediate is a methoxy acetal

from which the omega side chain, which is constructed by a conjugate coupling reaction, then the alpha side chain is formed by a Wittig reaction [16–18]. For reviews of prostaglandin syntheses see refs. [19–21]. Scheme 1 shows the structures of the key intermediates of the prostaglandin synthesis and the structures of $PGF_{2\alpha}$ and an isoprostane, $IPF_{2\alpha}$.

Explanation	Protected Corey lactone (−)-**5**	Protected cyclopentenone	Methoxy acetal
Name of key intermediates R = protecting group			
Structure of $PGF_{2\alpha}$		alpha side chain omega side chain	
Structure of $IPF_{2\alpha}$ 8-*iso*-$PGF_{2\alpha}$		In isoprostanes (IP-s) the side chains are attached to the cyclopentane ring in *cis* position	

Scheme 1. Key intermediates of prostaglandin syntheses and structures of $PGF_{2\alpha}$ and $IPF_{2\alpha}$.

Versatile chemical syntheses from widely available starting materials have removed barriers from the use of natural prostaglandins and synthetic derivatives in human [19] and veterinary therapies [22,23]. The main uses in human therapy are treatments of ocular hypertension and glaucoma [24,25], pulmonary arterial hypertension (PAH) [26,27], lumbar spinal stenosis [28], gastric and duodenal ulcer [29], labor induction [30], congenital heart disease in infants [31,32], and chronic idiopathic constipation [33].

The selection of successful drug candidates required the preparation of thousands of prostaglandin derivatives, among them the enantiomers and epimers of natural prostaglandins as well. The idea that enantiomers of natural prostaglandins retain their biological activity but metabolize in vivo more slowly has led to contradicting results; therefore, no drugs have been developed from the prostaglandin enantiomers and the interest in these derivatives has been pushed to the periphery [34–42]. The situation changed when Morrow and Roberts reported that prostaglandin-like compounds are generated in vivo from arachidonic acid by the peroxidation of free radicals independently of the cyclooxygenase pathway [43–47]. Unbalanced free radicals, reactive oxygen or nitrogen species (ROS or RNS), can cause oxidative stress in the body, contributing to the development of cardiovascular, neurological, respiratory, and kidney disease, and even cancer [48].

Once discovered, isoprostanes are used as important biomarkers to study the oxidative processes in humans. Prostaglandin enantiomers, which, unlike natural prostaglandins, are also formed from arachidonic acid by free radical reactions, are in the spotlight again as promising biomarkers.

2. Aim of the Work

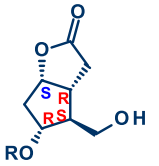
Evaluation of the literature data revealed that syntheses providing enantiomers of natural prostaglandins in a larger quantity are still missing. The aim of our work is to prepare prostaglandin enantiomers in a practical way using our processes that yield numerous prostaglandin active pharmaceutical ingredients in our prostaglandin plants.

The enantiomeric forms of natural prostaglandins can be used for scientific purposes as reference standards for studying oxidative processes in the body. Natural prostaglandins are synthesized from

arachidonic acid by COX-1/COX-2 enzymes. In contrast, enantiomers of the natural prostaglandins can be formed by free radical oxidation.

Another important application of enantiomeric forms is in the analytical tests of the prostaglandin active ingredients. The enantiomeric forms can be used as analytical standards to verify the optical purity of the active ingredients to ensure the quality that meets the requirements of the pharmaceutical authorities.

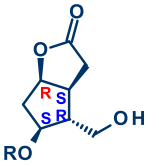
We plan to prepare the enantiomeric forms of all prostaglandins that are in our portfolio. This work has been started by synthetizing the enantiomeric forms of the natural prostaglandins that are manufactured in our plants, because they can be used for two different purposes. Hereinafter, enantiomeric forms of the modified prostaglandin derivatives will be prepared. The latter can only be used for analytical purposes, as they are not synthesized in the human body. In the present study, the synthesis of *ent*-$PGF_{1\alpha}$, *ent*-$PGF_{2\alpha}$, *ent*-PGE_2 and *ent*-PGE_1, starting from *ent*-Corey lactone, and methods for the separation of the enantiomeric pairs by chiral analytical HPLC are presented. See structures of the Corey lactone enantiomers ((−)-**5** and (+)-**5**)) and the prepared *ent*-prostaglandins in Scheme 2.



Corey lactone (R = protecting group)

(−)-**5**

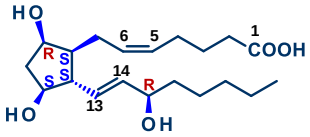
starting material of natural prostaglandins



ent-Corey lactone (R = protecting group)

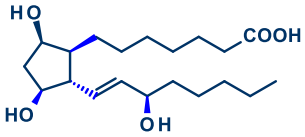
(+)-**5**

starting material of the mirror images, *ent*-PGs



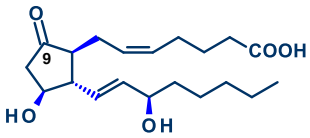
***ent*-$PGF_{2\alpha}$**

(−)-**1**



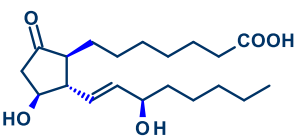
***ent*-$PGF_{1\alpha}$**

(−)-**3**



***ent*-PGE_2**

(+)-**2**



***ent*-PGE_1**

(+)-**4**

Scheme 2. Structure of Corey lactone enantiomers and *ent*-$PGF_{1\alpha}$, *ent*-$PGF_{2\alpha}$, *ent*-PGE_2 and *ent*-PGE_1.

3. Material and Methods

The commercially available reagents and analytical grade solvents were purchased from Merck (Darmstadt, Germany). Merck DC Fertigplatten 60 silicagel TLC plates with fluorescence indicator 254 nm was used for TLC chromatography, and Merck silica gel 60 (0.063–230 mm) for column chromatography.

Waters HPLC system equipped with a PDA detector and Empower V3 electronic data processing system was used for the HPLC method development.

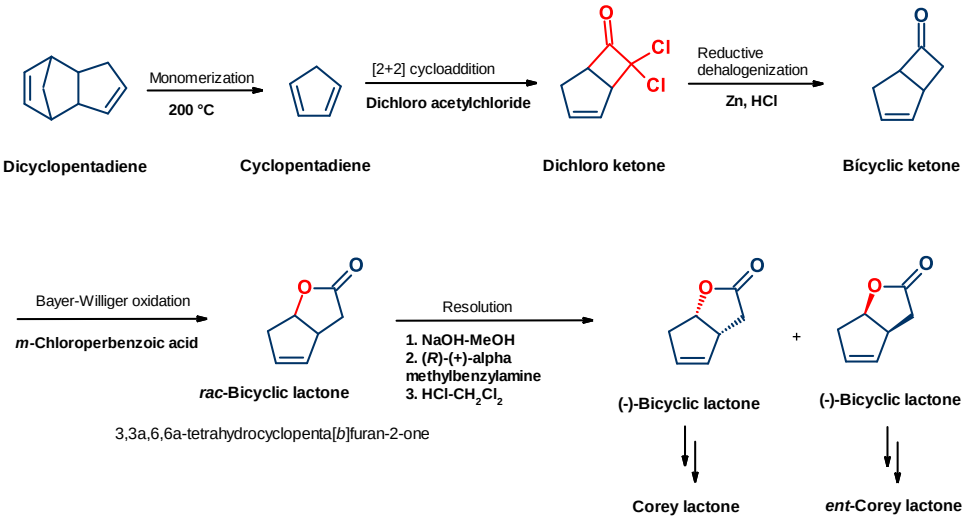
^{1}H and ^{13}C NMR spectra were recorded on Bruker AvanceIII (Billerica, MA, USA) instrument at 500.15 MHz and 125.8 MHz, respectively, in the DMSO-d_6 solvents. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS, coupling constants (*J*) in hertz (Hz). The solvent signals were used as references and the chemical shifts converted to the TMS scale (deuterated dimethyl sulfoxide

(DMSO-d_6): δC 39.52 ppm (sep) in DMSO-d_6, δH 2.50 ppm (m), residual peak in DMSO-d_6) [49]. In the report, the full assignment of the ^{1}H and ^{13}C NMR spectra have been achieved by utilizing the attached proton test (APT) and the two-dimensional HSQC, ed-HSQC, HMBC, COSY, NOESY and ROESY measurements.

4. Results and Discussions

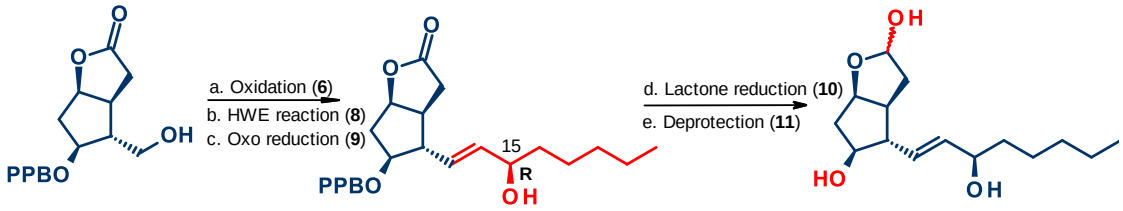
4.1. Synthesis of Mirror Images of Natural Prostaglandins

In our prostaglandin plant, we use modified version of Corey synthesis [48] to produce a variety of natural and structurally modified prostaglandins as active pharmaceutical ingredients (PG API-s) [50–69]. This versatile synthesis allows the production of different types of prostaglandins from a common intermediate, the Corey lactone ((−)-**5**). The same strategy was used to design the synthesis of enantiomeric forms of natural prostaglandins. Logically, in this case, the starting material was the mirror image of the Corey lactone, called *ent*-Corey lactone ((+)-**5**), from which each of the four enantiomeric prostaglandins could be prepared. The *ent*-Corey lactone can be synthetized by known methods from (+)-bicyclic lactone, the "wrong" enantiomer of the resolution step of the prostaglandin synthesis [48,70,71]. Preparation and resolution of *rac*-bicyclic lactone is shown in Scheme 3. The *ent*-Corey lactone and Corey lactone are also commercially available [72].



Scheme 3. Preparation and resolution of *rac*-bicyclic lactone.

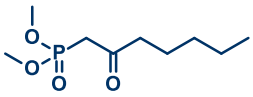
The initial reaction steps in the synthesis of *ent*-prostaglandins, were the transformation of the *ent*-Corey lactone ((+)-**5**) to the unprotected lactol (**11**). First, the primary hydroxyl-group in the *ent*-Corey lactone ((+)-**5**) was oxidized by Anelli oxidation [73]. Dichloromethane solution of the crude aldehyde (**6**) was reacted with the sodium salt dimethyl (2-oxo)heptylphosphonate (**7**) to form the omega side chain under the conditions of Horner–Wadsworth–Emmons (HWE) reaction [74–76]. Protected enone (**8**) was purified by crystallization. Then, the 15-oxo-group was stereoselectively reduced with in situ prepared catecholborane in the presence of (*S*)-2-Methyl-CBS catalyst [77]. After work-up, the lactone group of protected enol (**9**) was reduced to the lactol (**10**). The undesired diastereomer, the derivatized side-product of 15-oxo-reduction, (*S*)-**10** was removed by chromatography and crystallization. The methanolysis of PPB-protecting group provided the unprotected lactol (**11**), which was purified by crystallization. Reaction steps are shown in Scheme 4.



(+)-**5** **9** **11**

PPB- = p-phenylbenzoyl group

dimethyl (2-oxoheptyl)phosphonate (**7**)



Scheme 4. Preparation of lactone (11) from *ent*-Corey lactone (+)-**5**. (**a**) NaOCl, KBr, NaHCO3, TEMPO catalyst, dichloromethane, water, 0–10 °C; (**b**) **7**, NaOH, dichloromethane, water, 0–10 °C, crystallization from diisopropyl ether-hexane; (**c**) BH3-DMS, pyrocatechol, (S)-2-Me-CBS, THF, (−15)–(−10) °C; (**d**) DIBAL-H, THF, toluene, (−75)–(−70) °C, chromatography with toluene-EtOAc, crystallization from toluene-hexane; (**e**) K2CO3, MeOH, 35–40 °C, crystallization from EtOAc-diisopropyl ether.

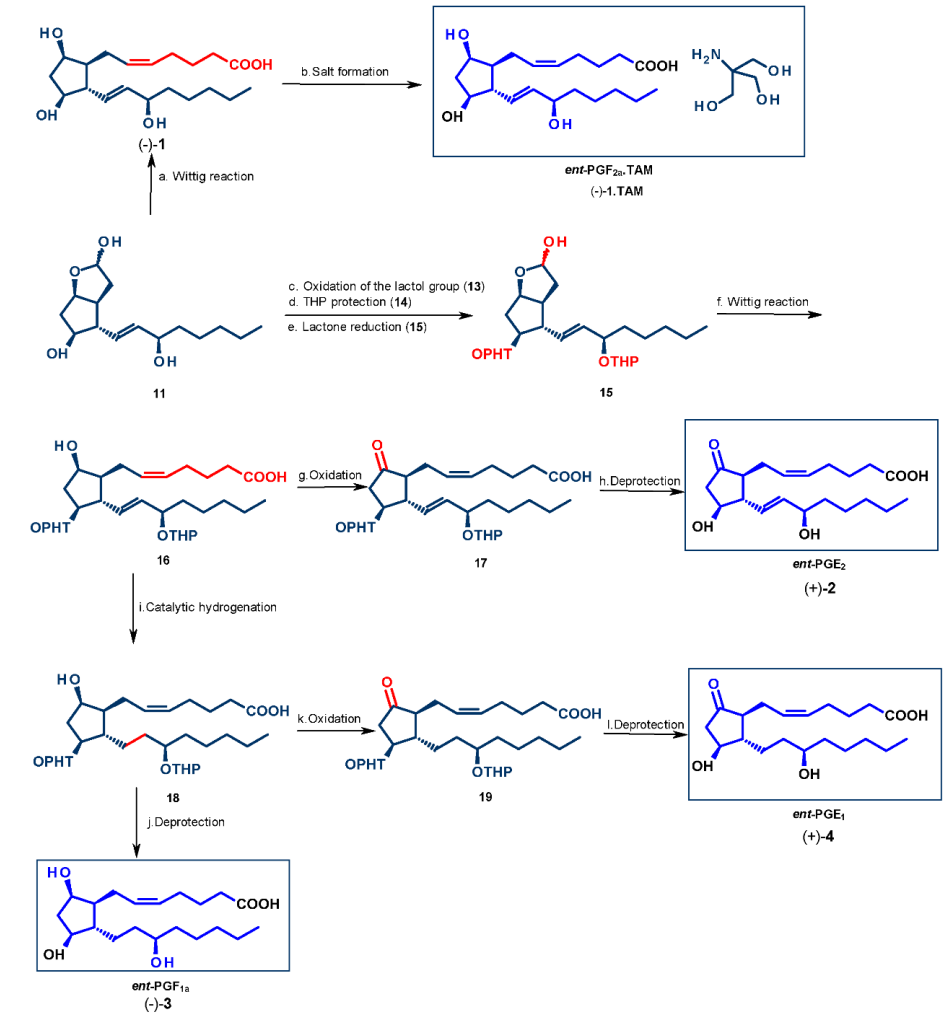
The unprotected lactol (**11**), containing a masked aldehyde functionality, is a common building block of all four enantiomeric prostaglandins. The alpha side chain for *ent*-$PGF_{2\alpha}$ ((−)-**1**) was prepared by Wittig reaction with the phosphorane liberated from 4-carboxybutyl triphenylphosphonium bromide (CBP-Br) (**12**) by the strong base, $KOBu^t$. We have not crystallized yet the oily crude *ent*-$PGF_{2\alpha}$ (**1**), instead it was converted to its stable, crystalline tromethamine salt.

For the preparation of the remaining three derivatives *ent*-PGE_2 ((+)-**2**), *ent*-$PGF_{1\alpha}$ ((−)-**3**), ent-PGE_1 ((+)-**4**), the lactol group of **11** was reoxidized to lactone (**13**) with iodine in an aqueous medium containing KI and $KHCO_3$. This reoxidation is required for the selective formation of the 9-oxo group in the PGE derivatives. Free hydroxyl groups were protected with dihydropyran by an acid catalyzed reaction, supplying the bis-THP lactone (**14**). To form the alpha side chain of the prostaglandin structure, the lactone group was reduced to lactol to make the molecule suitable for the Wittig reaction. The alpha side chain was built again with the phosphorane prepared from CBF-Br (**12**) with $KOBu^t$ as the base in THF solution, giving the *ent*-THP_2-$PGF_{2\alpha}$ (**16**), that is the last common intermediate for the preparation of *ent*-PGE_2 ((+)-**2**), *ent*-$PGF_{1\alpha}$ ((−)-**3**) and *ent*-PGE_1 ((+)-**4**).

Preparation of *ent*-PGE_2 ((+)-**2**), happened by the oxidation of the free 9-hydroxyl group of acid (**16**) with pyridinium chlorochromate (PCC) in ethyl acetate. The pH of the reaction mixture was buffered by sodium acetate and acetic acid. The crude *ent*-THP_2-PGE_2 (**17**) was filtered through silica gel to remove the residue of the oxidant. In the last step of this series, the THP-protecting groups were removed in isopropanol. The reaction was catalyzed by 1 mol/L hydrochloric acid. Crude *ent*-PGE_2 ((+)-**2**) was purified by chromatography using hexane-ethyl acetate eluent, and crystallization from ether-diisopropyl ether.

To prepare *ent*-$PGF_{1\alpha}$ ((−)-**3**) and *ent*-PGE_1 ((+)-**4**) the *cis* double bound in the alpha side chain of **16** must be selectively reduced. This selective reduction is a key step because it allows derivatives containing either one or two double bonds to be prepared from a common intermediate. This transformation is performed by catalytic hydrogenation in diisopropyl ethylamine-dichloromethane solution using 10% Pd/C catalyst. The quantity of crude *ent*-THP_2-$PGF_{1\alpha}$ (**18**) was divided into two parts. One part was dissolved in isopropanol containing 1 mol/L hydrochloric acid to remove the THP-protecting groups, giving *ent*-$PGF_{1\alpha}$. Crude *ent*-$PGF_{1\alpha}$ ((−)-**3**) was purified by double crystallization from ethyl acetate followed by ethyl acetate-hexane.

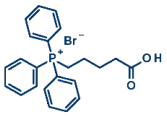
The 9-hydroxyl group of the remaining quantity of **18** was oxidized with PCC to the 9-oxo derivative, *ent*-THP_2-PGE_1 (**19**). Crude **19** was purified by column chromatography. The evaporated main fraction was dissolved in isopropanol containing 1 mol/L hydrochloric acid to remove the protecting groups. Crude *ent*-PGE_1 ((+)-**4**) was crystallized from diisopropyl ether-hexane. Reaction steps for the preparation of *ent*-prostaglandins are shown in Scheme 5.



THP- = tetrahydropyranyl group

TAM = **t**romethh**am**ine (trisaminomethane)

CBP-Br



Scheme 5. Preparation of *ent*-prostaglandins from lactol **11**. (**a**) CBP-Br, $KOBu^t$, THF, (−10)-(−5) °C; (**b**) TAM, MeOH, acetone, hexane, 25 °C→ 0 °C; (**c**) I_2, KI, $KHCO_3$, water; (**d**) Dihydropyran, pTsOH.H_2O, toluene, THF, 20–50 °C; (**e**) DIBAL-H, toluene, THF (−75)–(−70) °C; (**f**) CBP-Br, $KOBu^t$, THF, toluene, (−10)–(−5) °C; (**g**) PCC, NaOAc, AcOH, EtOAc, 30–40 °C, chromatography with diisopropyl ether-acetone mixture as eluent; (**h**) 1 mol/L HCl, H_2O, *i*-PrOH, 20 °C, chromatography with hexane-EtOAc mixtures as eluent, crystallization from ether-diisopropyl ether; (**i**) cat H_2, Pd/C, diisopropyl ethylamine, dichloromethane, rt; (**j**) 1 mol/L HCl, H_2O, *i*-PrOH, 20 °C, crystallization from EtOAc then EtOAc-hexane; (**k**) PCC, NaOAc, EtOAc, AcOH, 30–40 °C, chromatography with diisopropyl ether-EtOAc mixture as eluent; (**l**) 1 mol/L HCl, H_2O, *i*-PrOH, 20 °C, crystallization from diisopropyl ether-hexane.

4.2. Separation of Natural Prostglandin Enantiomers by Chiral HPLC

Having the optically pure mirror images of four natural prostaglandins in our hands (chemical purities are given in the Supplementary Material), the next goal was to develop chiral HPLC methods for the separation of the enantiomeric pairs. To date, only one scientific article has reported the chiral reversed phase HPLC separation of PGE_2 enantiomers. According to the article, various chiral HPLC columns were tested, but the enantiomeric separation was only successful when the Phenomenex Lux Amylose2 column was used. Elution of the Lux Amylose2 column with methanol:water or 2-propanol:water did not resolve the enantiomers. When a low concentration of acetonitrile (25% in water with 0.1% formic acid) and a slow flow rate (50 µL/min) were used, the enantiomers separated, but the peaks were broadened. The best results were obtained when two columns, connected in series were used for the enantiomeric separation [78].

As the known procedure presented a rather sophisticated method and that method was only applied for the separation of PGE_2 enantiomers, we have decided to work out a simplified procedure which is suitable for routine tests of the prostaglandins manufactured in our plant.

Reverse phase methods are promising for the chromatographic analysis of acidic compounds, including prostaglandin acids, so we have been looking for a reverse phase chiral column. Based on literature data and our previous experience, we have chosen Chiracel OJ-RH as the chiral HPLC column. This type of column has been successfully applied for the enantiomeric separation of chemically distinct racemic organic acids [79].

In selecting the values of the test parameters, we partly took into account the column supplier's recommendation [80], and partly our chromatographic experience. The reversed phase HPLC conditions are summarized in Table 1.

Table 1. Reversed phase HPLC conditions.

Parameter	Value
Apparatus:	Waters HPLC system equipped with a PDA detector and Empower V3 electronic data processing system
Column:	Chiracel OJ-RH, 150 × 4.6 mm, 5 µm
Column temperature:	25 or 40 °C (5–40 °C) *
Flow rate:	0.5 mL/min (0.5–1.0 mL) *
Injected volume:	5 µL
Concentration of sample:	0.25 mg/mL
Composition of eluent:	see Table 2
Composition of sample solvent:	acetonitrile:methanol:water 30:10:60
Wavelength:	200, 210 nm
Run time:	20–40 min

* The optimal parameters recommended by the column supplier are shown in the brackets.

Based our preliminary experiments, sample solutions were prepared by dissolving equal amounts of the pure enantiomers in the sample solvent (acetonitrile:methanol:water = 30:10:60) and aliquots from the solution of the corresponding enantiomeric pairs were mixed prior to the injection. The eluent was a three-component mixture containing acetonitrile:methanol:water (pH = 4). It is noted here that pH of the water was adjusted to 4 with phosphoric acid (85 *w*/*w*% in H_2O) in every case. This pH = 4 value provides an adequate separation and elution rate for the prostaglandin acids, without causing decomposition of their acid-sensitive structure. Phosphoric acid was also recommended for adjusting the pH of Chiracel OJ-RH columns at this pH value to avoid degradation of the column. Composition of the eluents were varied in a wide range to achieve a good resolution. The composition of the eluents is summarized in Table 2.

Table 2. Eluent composition.

Run	Composition		
	Acetonitrile	**Methanol**	**Water (pH = 4)**
1	30	10	60
2	25	10	65
3	24	10	66
4	23	10	67
5	20	10	70
6	20	15	65
7	15	20	65
8	15	15	70

The results for individual runs were evaluated by comparing the resolution values (R) calculated according to United States Pharmacopeia (USP-NF, < 621 > Chromatography). To achieve at least R = 1.2 resolution the composition of the eluent and column temperature were varied. When optimizing the method, not only the resolution, but also the time and eluent consumption were taken into account. The effect of the variable parameters on the resolution of enantiomers of PGE_2 is shown in Figure 1.

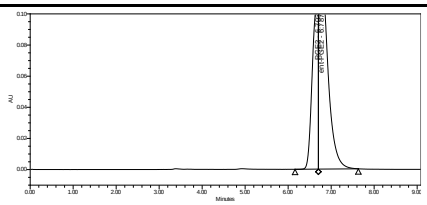
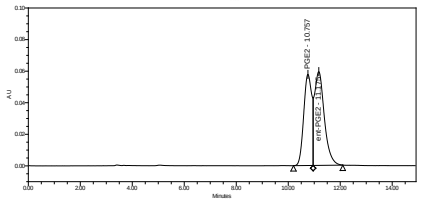
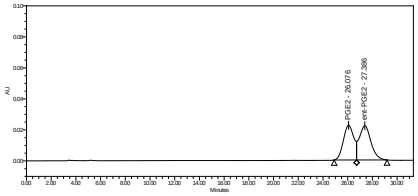
Parameters				**Resolution**	**Result**
Eluent			**Column**	***R***	
MeCN	**MeOH**	**H_2O**	**T (°C)**		
30	10	60	25	-	
25	10	65	25	-	
20	10	70	25	-	

Figure 1. *Cont.*

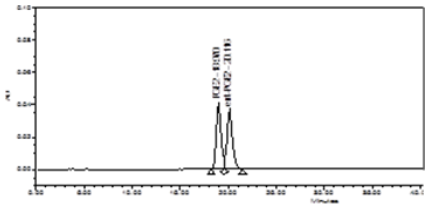
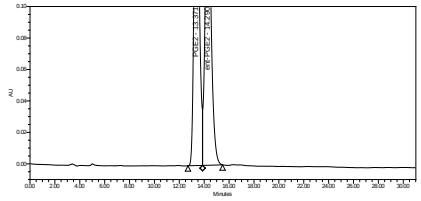
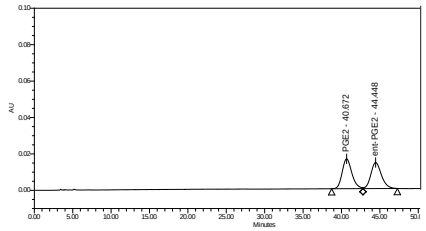
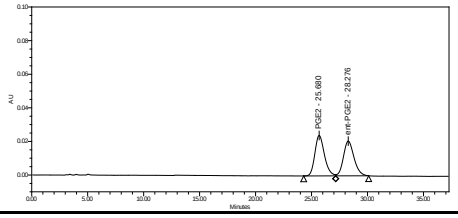
20	10	70	40	1.1	
20	15	65	40	1.2	
15	15	70	40	1.5	
15	20	65	40	1.6	

Figure 1. Effect of the variable parameters on the resolution of PGE_2 enantiomers.

By varying the indicated parameters, we performed the chiral separation of all four enantiomeric pairs with excellent resolution, $R \geq 1.5$. The best resolutions are shown in Figures 2–5.

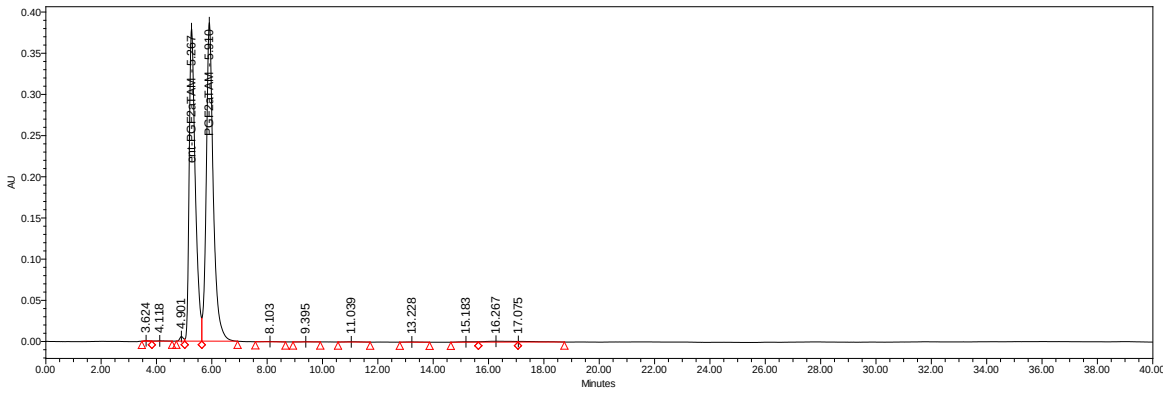


Figure 2. Chiral separation of the optical isomers of $PGF_{2\alpha}$ (tested as TAM salt), $R = 1.5$. Optimized parameters: Eluent: MeCN:MeOH:water (pH = 4) = 30:10:60, column temperature 25 °C, wavelength 200 nm.

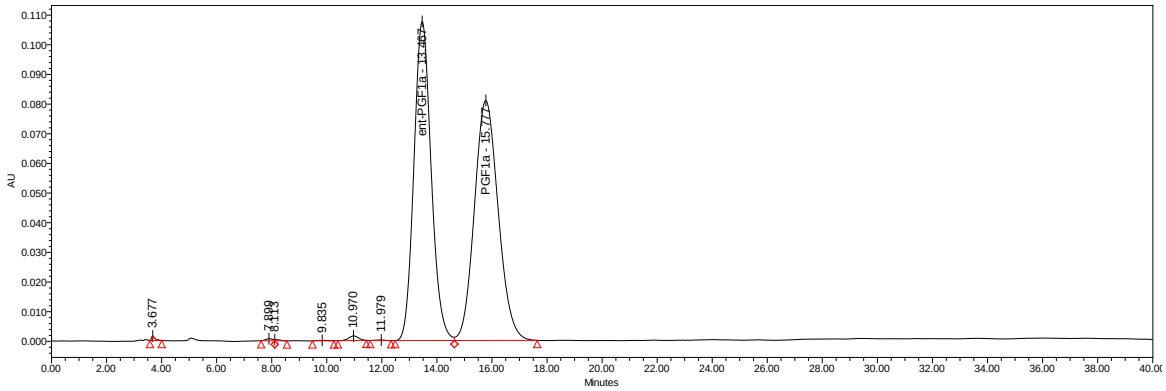


Figure 3. Chiral separation of the optical isomers of $PGF_{1\alpha}$, R = 1.7. Optimized parameters: Eluent: MeCN:MeOH:water(pH = 4) = 23:10:67, column temperature 25 °C, wavelength 200 nm.

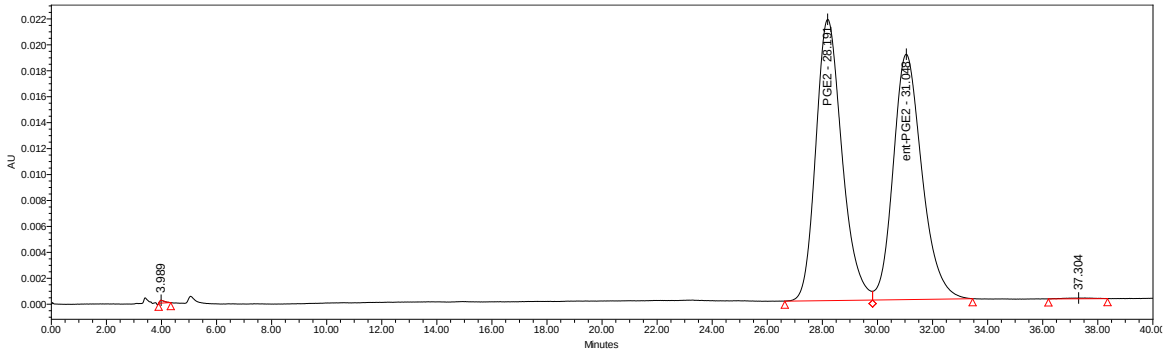


Figure 4. Chiral separation of the optical isomers of PGE_2, R = 1.5. Optimized parameters: Eluent: MeCN:MeOH:water(pH = 4) = 15:20:65, column temperature 40 °C, wavelength 210 nm.

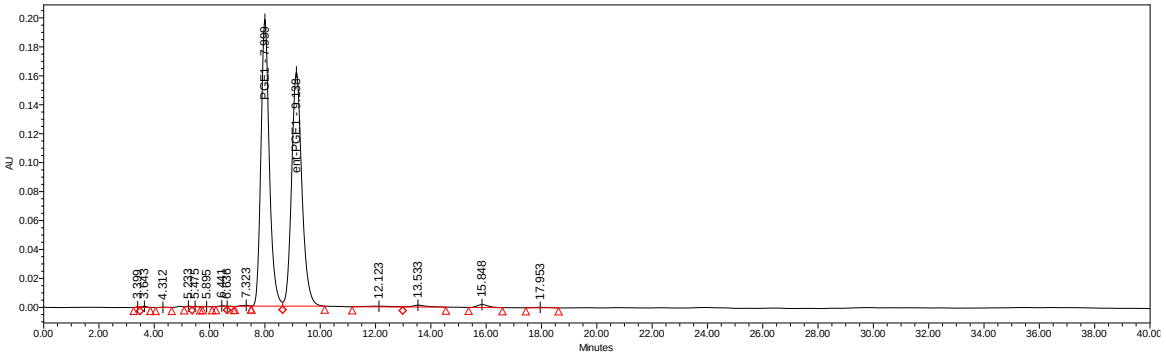


Figure 5. Chiral separation of the optical isomers of PGE_1, R = 1.8. Optimized parameters: Eluent: MeCN:MeOH:water(pH = 4) = 30:10:60, column temperature 25 °C, wavelength 200 nm.

Enantiopurity of the individual pure *ent*-prostaglandins has been also determined by the developed chiral methods. HPLC area percentages and enantiomeric excesses are summarized in Table 3.

Table 3. Enantiopurity of the *ent*-prostaglandins.

***ent*-PG**	**HPLC Area %**	**Enantiomeric Excess**
ent-PGF_{2a}.TAM (−)-**1**.TAM	98.2	0.964
ent-PGE_2 (+)-**2**	99.9	0.998
ent-$PGF_{1\alpha}$ (−)-**3**	99.3	0.986
ent-PGE_1 (+)-**4**	99.9	0.998

5. Conclusions

Four mirror images of the natural prostaglandins, *ent*-$PGF_{2\alpha}$ ((−)-**1**), *ent*-PGE_2 ((+)-**2**), *ent*-$PGF_{1\alpha}$ ((−)-**3**), and *ent*-PGE_1 ((+)-**4**) were synthesized by the modified Corey synthesis. The starting material was the *ent*-Corey lactone ((+)-**5**), which is a side-product of our prostaglandin production. Using *ent*-Corey lactone ((+)-**5**) the mirror images of natural prostaglandins and numerous modified derivatives can be synthesized. The mirror images of prostaglandins can be used as reference standards to justify the optical purity of the pharmaceutical active ingredients. In addition, enantiomeric forms of natural prostaglandins may be important biomarkers to study the oxidative stress of the human body to better understand the mechanism of development of many serious, or even fatal, diseases.

Chiral HPLC methods have been also developed for the analytical separation of the enantiomeric pairs. Enantiopurity of the pure *ent*-prostaglandins has been determined. The HPLC method developed proved to be quite general. The Chiracel OJ-RH column was suitable for the separation of all four enantiomeric pairs. The eluent mixture contained acetonitrile:methanol:water (pH = 4) in each case, but the solvents were mixed in different proportions. The column temperature was 25 °C for the separation of the enantiomeric pairs of $PGF_{2\alpha}$, $PGF_{1\alpha}$ and PGE_1, but adequate resolution of the PGE_2 enantiomers was achieved at a higher column temperature, at 40 °C.

In contrast to the known method, the procedure developed is suitable for the routine analytical tests to check the enantiopurity of the prostaglandins produced in our plants.

Our long-term goal is to synthesize the mirror images of all prostaglandins that are in our portfolio in order to test the enantiopurity of the active ingredients of the prostaglandin drugs.

Supplementary Materials: Preparation of *ent*-$PGF_{2\alpha}$ ((−)-**1**), *ent*-PGE_2 ((+)-**2**) *ent*-$PGF_{1\alpha}$ ((−)-**3**), and *ent*-PGE_1 ((+)-**4**) is available online at http://www.mdpi.com/2624-8549/2/3/47/s1.

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