

# Synthesis of Novel Heterocyclic Prostaglandin Analogues

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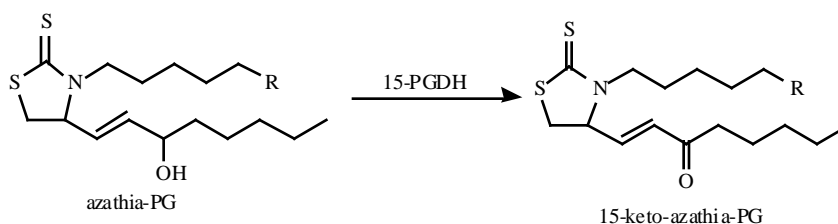
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**Abstract:** New prostaglandins analogues, containing heteroatoms in the cyclopentane ring were synthesized. The key step in the synthesis was the preparation of the five-membered ring starting from L-cysteine ethyl ester hydrochloride. The addition of the alkyl groups at C-15 position was also performed.

**Keywords:** Heterocyclic prostaglandins, azaprostaglandins, thiaprostaglandins.

Prostaglandins analogues containing heteroatoms in the ring have received a great deal of attention due to their potential biological properties, [1-4] diversified biological activity and rapid metabolism of the naturally occurring prostaglandins. Particularly interesting is that these prostaglandins containing heteroatoms in the ring can act as both gastric-acid secretion and platelet aggregation inhibitors. In this article, we report a total synthesis of new prostaglandins analogues in which the oxygen carbonyl at C-9 was substituted by a sulfur atom and the addition of the alkyl groups at C-15 position was made through the Grignard reagents, in the presence of cerium chloride. This step was performed to prevent the fast 15-hydroxy function oxidation caused by the enzyme prostaglandin-15-

[7]. *N*-Alkylation of the thiazolidine ether (**4**) was carried out by using the procedure described by Zoretic and Soja [8]. Reaction of the sodium salt of **4** with alkyl halides THF at 50 °C under nitrogen, afforded the *N*-alkylated thiazolidine ether (**5**) [9]. The alkyl derivative **5** thus obtained was treated with pyridinium *p*-toluenesulfonate (PPTS) in ethanol, yielding the deprotected thiazolidine alcohol (**6**) [7]. Oxidation of the compound **6** with Swern reagent [10] in methylene chloride at -60 °C under nitrogen atmosphere followed by addition of water, solvent evaporation and a rapid filtration of the reaction mixture on silica gel G, afforded the aldehyde (**7**) with low yield (c.a. 55%). Reaction of the aldehyde (**7**) with the lithium salt of dimethyl-(2-oxoheptyl) phosphonate in tetrahydrofuran at 0



**Fig. (1).**

dehydrogenase in the primary deactivation step of the prostaglandin metabolism. In this step the 15-allylic alcohol is interconverted to the less active 15-keto-PG [13], as shown in Fig. (1).

The reaction of L-cysteine ethyl ester hydrochloride (**1**) with carbon disulfide in the presence of triethyl amine in  $\text{CH}_2\text{Cl}_2$  at room temperature, afforded the appropriate functionalized intermediate **2** [5]. ( $[\alpha]_D^{25} = -73^\circ$  (1.0,  $\text{CHCl}_3$ ). Reduction of the thiazolidine ester (**2**) with an excess of sodium borohydride in boiling methanol in the presence of *t*-butanol, yielded the thiazolidine alcohol (**3**). The protection of the primary hydroxy group present in **3** was accomplished by using dihydropyran in the presence of a catalytic amount of *p*-toluenesulfonic acid in methylene chloride–tetrahydrofuran, yielded the thiazolidine ether (**4**)

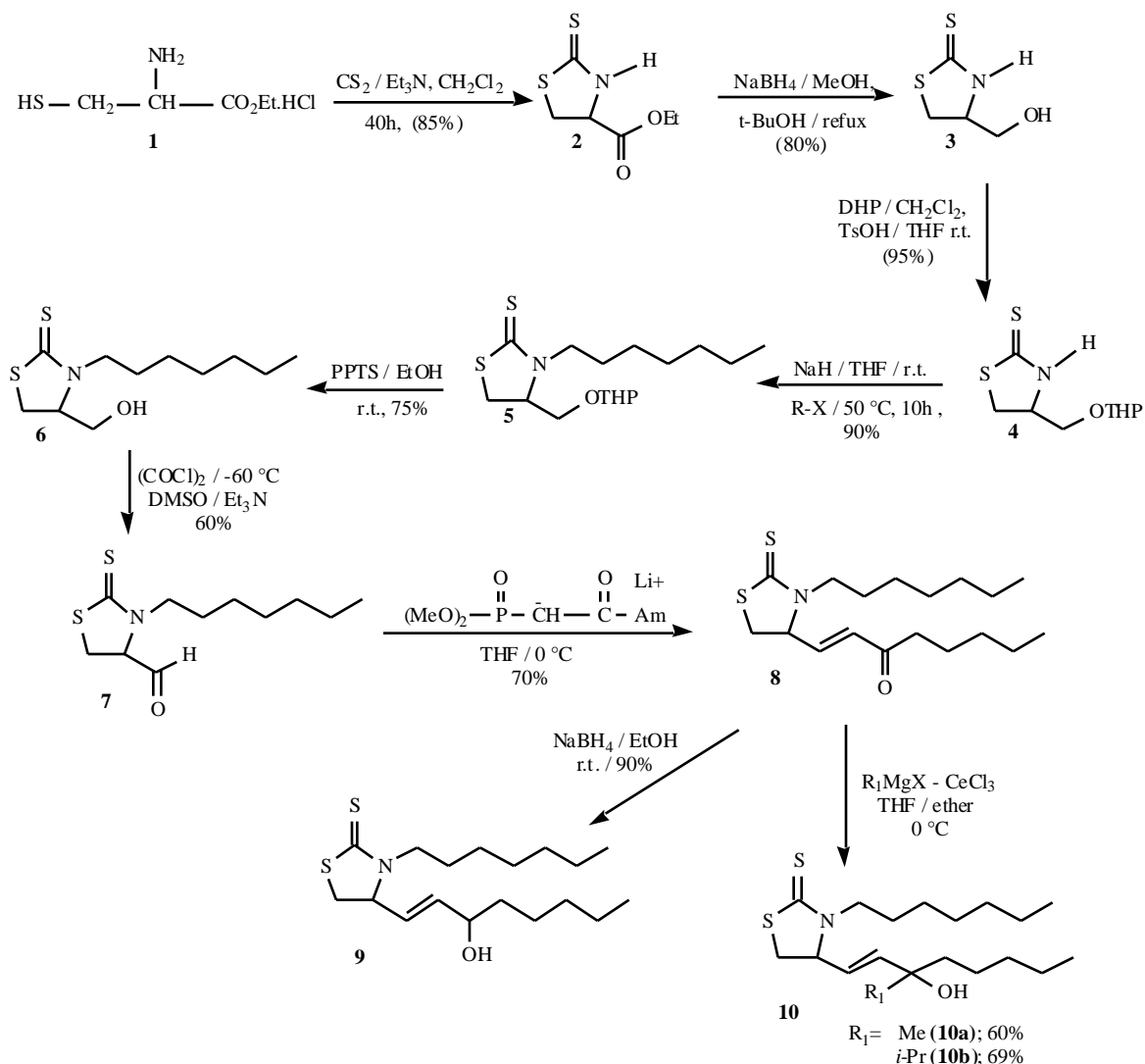
°C for 3 h, gave the enone (**8**) [11]. Non stereoselective reduction of the enone afforded the heterocyclic prostaglandins (**9**) [9]. In the presence of anhydrous cerium (III) chloride, Grignard reagents react with enone **8** to afford a diastereomeric mixture of tertiary alcohols (**10a,b**) [12].

The route for the synthesis of this new azathia-PG's is shown in Scheme 1.

In summary, the synthetic sequence developed in this work for obtaining new azathia-PG analogues starting from an easily accessible compound is described. An easy five-membered ring formation from L-cysteine ethyl ester hydrochloride serves as a key for further functional groups interconversions.

Other azathia-PG analogues **10** reactions with modified -side chains are still in progress in our laboratory. The racemic mixture of **10a,b** will be tested as possible bronchodilators compounds. The biological activity of this compounds as possible platelet aggregators or inhibitors will also be verified.

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Scheme 1.

### General Procedure for the Preparation of Prostaglandin 10b

Cerium chloride ( $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ ) (0.14 g, 0.55 mmol) was placed in a 25 mL flask. Most of crystallization water was removed in a Abderhalden drying apparatus at  $120 }^\circ\text{C}$  for 3 h. Tetrahydrofuran (5 mL) previously dried was added with stirring and the suspension was stirred for 2 h at room temperature. The flask was again immersed in ice bath and isopropylmagnesium bromide, previously prepared by adding 2-bromopropane (0.044 g; 0.55 mmol) in THF anhydrous over magnesium turnings in the presence of anhydrous THF, was added. After stirring for 1.5 h at  $0 }^\circ\text{C}$ , enone (**8**) (0.17 g; 0.43 mmol) was added and stirring was continued for 1 h. The reaction mixture was treated with 10 mL of a solution containing water (50 mL) and acetic acid (2 mL). The mixture was extracted with ether (3x30mL), and the combined extracts were washed with brine (30mL), 5% sodium bicarbonate solution (20mL), brine (30mL), and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residual oil underwent a chromatographic process on silica gel G, eluting with hexane:acetone solution (8:2) to give 0.13 g (69%) of **10b** as a viscous oil:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 6.05-5.90 (m,

1H); 5.65-5.25(m, 2H); 4.50-4.13(m, 2H); 3.84 (sl, 1H-OH); 3.35(t, 2H); 1.75(m, 1H-*i*-Pr); 0.98-0.85(d, 6H-*i*-Pr); 0.87-0.80(t, 6H).  $\text{NMR}^{13}\text{C}$  ( $\text{CDCl}_3$ ): 173.75(s); 140.5(d); 130.2(d); 80.3(s); 76.5(d); 53.5(t); 43.3(t); 36.2(d); 24.6(q); 19.3(q); 14.2(q) and 14.6(q). Microanalyses: C, 65.30; H, 09.50; N, 3.57%. **Compound 10a** -  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 5.99 (dd, 1H); 5.71(d, 1H); 4.85-4.70(m, 1H); 4.18-4.02(m, 2H); 3.60 (sl, 1H-OH); 3.25(t, 2H); 1.37(s, 3H- Me); 0.95(t, 3H).  $\text{NMR}^{13}\text{C}$  ( $\text{CDCl}_3$ ): 185.0(s); 130.2(d); 122.0(d); 72.5(d); 67.2(s); 52.5(t); 43.3(t); 42.1(t); 26.5(q); 13.9(q) and 14.5(q). Microanalyses: C, 61.97; H, 10.0; N, 3.90%.

**Compound 3**:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 4.34-4.44(m, 1H); 3.63-3.81 (m, 3H); 3.47-3.52 (dd, 1H,  $J=6.6$  e 5.9 Hz); 2.89 (sl, 2H). Microanalyses: C, 32.3; H, 4.70; N, 9.52%.  $^{25}\text{D} = +30^\circ$  (1.0,  $\text{CHCl}_3$ ); mp  $102\text{-}103 }^\circ\text{C}$ . **Compound 4**:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.32 (sl, 1H); 4.63-4.67 (m, 1H); 4.46-4.50 (m, 2H); 3.77-3.91 (m, 2H); 3.50-3.69 (m, 3H); 1.25-1.85 (m, 6H). Microanalyses: C, 45.97; H, 6.39; N, 5.45%. **Compound 5**:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 4.63-4.95 (m, 1H); 3.78-3.97 (m, 2H); 3.35-3.56 (m, 5H); 2.95-3.18 (m, 2H); 1.27-1.84 (m, 16H); 0.88(t, 3H). Microanalyses: C, 58.53; H, 8.66; N, 4.22%. **Compound 6**:  $^1\text{H NMR}$

(CDCl<sub>3</sub>): 4.50–4.63 (m, 1H); 3.67–3.79 (m, 2H); 3.29–3.64 (m, 2H); 3.04–3.14 (t, 3H); 1.61–1.75 (m, 2H); 1.20–1.50 (m, 8H); 0.89 (t, 3H). Microanalyses: C, 53.60; H, 8.43; N, 5.66%. <sup>25</sup>D<sub>D</sub>+37° (1.0, CHCl<sub>3</sub>). **Compound 7**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): 9.93 (s, 1H); 4.99–5.04 (dd, 1H); 3.65–3.77 (m, 1H); 3.25–3.51 (m, 1H); 3.29 (t, 2H); 1.15–1.78 (m, 10H); 0.88 (t, 3H). **Compound 8**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.27–7.47 (m, 1H); 6.82–7.14 (m, 1H); 3.25 (t, 2H); 3.03–3.10 (dd, 1H); 2.73–2.80 (dd, 1H); 2.63 (t, 2H); 1.13–1.83 (m, 16H); 0.88 (t, 6H). Microanalyses: C, 60.31; H, 8.18; N, 3.66%. **Compound 9**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.90–6.94 (m, 1H); 6.52–6.65 (m, 2H); 5.29 (sl, 1H); 4.13–4.31 (m, 2H); 3.20 (t, 2H); 2.05–2.11 (m, 1H); 1.25–1.84 (m, 18H); 0.88 (t, 6H). Microanalyses: C, 63.06; H, 09.20; N, 03.70%.

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