chemistry proceedings

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Abstract

Key Intermediates for Building the ω-Side Chain of Prostaglandins with a Constrained Pentalenofurane Scaffold Linked to C-15 Carbon Atom to Diminish the PG Inactivation †

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† Presented at the 17th International Symposium "Priorities of Chemistry for a Sustainable Development" PRIOCHEM, Bucharest, Romania, 27–29 October 2021.

Keywords: halogeno-pentalenofurane scaffold; pentalenofurane esters; penalenofurane-β-ketophosphonates; 15-bulky prostaglandin substituents; PGF1 analog; X-ray analysis

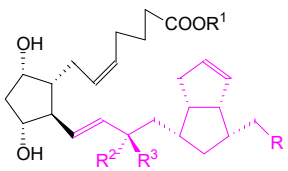
Citation: Tanase, C.; Draghici, C.; Caproiu, M.T.; Hanganu, A.; Borodi, G.; Maganu, M.; Gal, E.; Pintilie, L. Key Intermediates for Building the ω-Side Chain of Prostaglandins with a Constrained Pentalenofurane Scaffold Linked to C-15 Carbon Atom to Diminish the PG Inactivation. *Chem. Proc.* **2022**, *7*, 84. https://doi.org/10.3390/chemproc2022007084

Academic Editors: Mihaela Doni, Florin Oancea, Zina Vuluga and Radu Claudiu Fierăscu

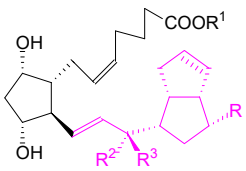
Published: 30 June 2022

1. Introduction

The inactivation of prostaglandin (PG) and prostaglandin analogs (PGs) is realized with enzyme oxidation of the 15α-OH to the 15-keto group via the 15-PGDH pathway. To slow down this oxidation, some structural modifications were made: the introduction of a 15-methyl group, a 16-OH,16-methyl group, two methyl groups at C_{16}, cyclopentyl and cyclohexyl scaffolds, etc [1]. In this direction, we previously introduced bicyclo[3.3.0]octene or bicylo[3.3.0]octane fragments in β-ketophosphonates [2,3] to obtain the PG analogs I and II (Figure 1), knowing that these fragments are encountered in natural products, some of them with anticancer activity.



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



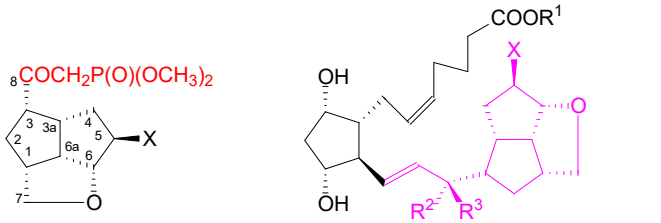
II. Prostaglandin analogues with a bicyclo[3.3.0]oct(a)ene fragment in the ω-side chain linked to C_{15} carbon atom

Figure 1. Prostaglandin analogues with a bicyclo[3.3.0]octene and bicyclo[3.3.0]octane fragments in the ω-side chain, of types **I** and **II**.

In the first compound, **I**, the bicyclo[3.3.0]octene fragment is linked to the C_{16} carbon atom, which is a small but significant hindrance of the 15-PGDH enzyme to inactivate the PG analogue via the oxidation of 15α-OH to the 15-keto group [2].

In the second compound, **II**, the bicyclo[3.3.0]octene and bicyclo[3.3.0]octane fragments linked to the C_{15} carbon atom are expected to slow down the inactivation of the PG analog [3].

Now, we present the synthesis of new key β-ketophosphonates **5**, with a more bulky pentalenofurane scaffold linked to the keto group to build type **III** PG analogues (Figure 2):



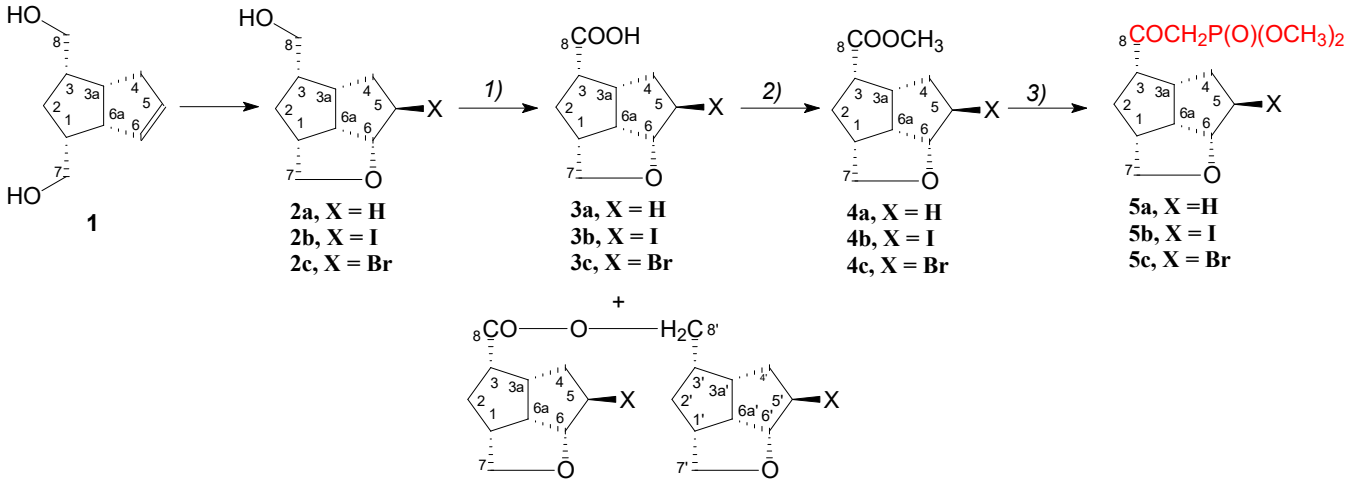
5. X = H, I, Br
β-ketophosphonates with a pentalenofurane fragment

III. Prostaglandin analogues with a pentalenofurane fragment in the ω-side chain linked to C_{15} carbon atom

Figure 2. β-Ketophosphonates **5** with a pentalenofurane fragment in the molecule to obtain new type **III** prostaglandin analogues.

2. Materials and Methods

Syntheses of the compounds were realized in three high-yield reactions, starting from the pentalenofurane alcohols **2**. The alcohols were oxidated with Johns reagent to the acids **3**, which were esterified to the methyl esters **4**. In the last step, the esters **4** were reacted with lithium salt of dimethyl methanephosphonate at a low temperature to give the β-ketophosphonates **5** (Scheme 1). The secondary compounds **6b** and **6c** were formed in small amounts in the Johns oxidation of **2b** and **2c**, and the NMR spectroscopy showed that their structure is that of an ester of the acid with the starting alcohol.



Scheme 1. Synthesis of pentalenofurane β-ketophosphonates **5a**–**5c**. *(1)* Jones reagent (2.4 M), acetone, −15 to 0 °C, **2a**, 81.8% **3a**; with **2b**, 85.15% **3b**; with **2c**, 73.7% **3c**, *(2)* MeOH, TsOH, rt, overnight, 86.4% **4a**; 92.4% **4b**; 81.0% **4c**, *(3)* dimethyl methanephosphonate, *n*-BuLi, −75 °C to −65 °C, 88.0% **5a**; 78.6% **5b**; 83.3 % **5c**.

Their molecular structures were confirmed using the single crystal X-ray determination method for **6c** and the XRPD powder method for **6b** (Figure 3):

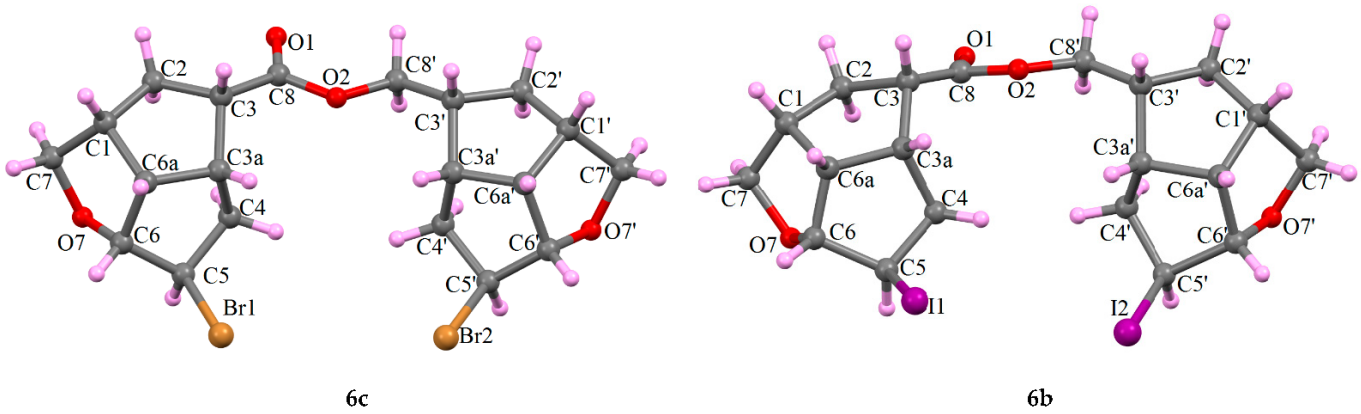
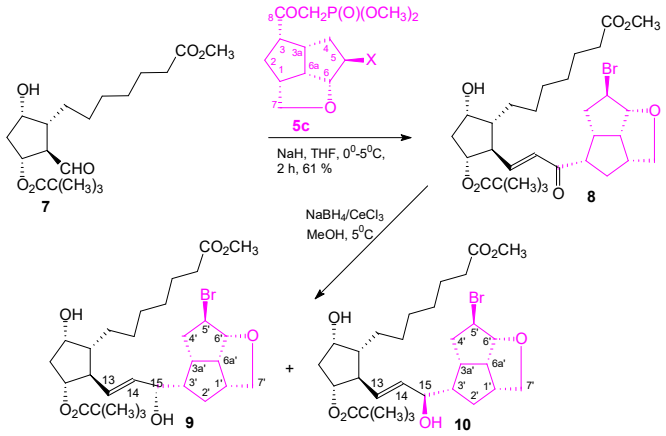


Figure 3. X-ray molecular configuration of the asymmetric unit of the secondary compounds **6c** and **6b**.

3. Results

Three key intermediate β-ketophosphonates **5** were synthesized in a high-yield, short-sequence synthesis, as presented in Scheme 1, and fully characterized. β-Ketophosphonate **5** was used to obtain type **III** PG analogs in the *E*-HEW selective olefination of the aldehyde **7**, with the hydrogenated α-side chain, to the ketoprostaglandin analog **8** (Scheme 2):



Scheme 2. Synthesis of F_1 PG analogs **8**, **9** and **10** with a pentalenofurane fragment in the ω-side chain.

The reduction of the enone group to the desired allylic alcohol **9** with the selective but bulky reducing reagent aluminum diisobornyloxyisopropoxide, usually used in the PG field, did not proceeded as in the case of the PG analog **II** (R^1,R^2 = O) (Figure 1), as expected. The Luche reduction of enone **8** with $NaBH_4$ and $CeCl_3$ gave the allylic alcohol **9** together with its 15-epimer, **10**, in a ratio of 1:1. As in the reduction, the bulky, constrained pentalenofurane scaffold in the ω-side chain was used to slow down the inactivation of the PGs analogs via the enzyme 15-PGDH pathway.

4. Conclusions

The synthesis of key β-ketophosphonates **5a–5c** with a pentalenofurane scaffold linked to the keto group was realized in a sequence of three high-yield reactions. Two by-products formed in the oxidation of alcohols **2** were characterized using NMR and confirmed using single crystal X-ray crystallography for **6c** and the XRPD powder method for **6b**. For the first time, the key intermediates **5** were used to obtain the PGF_1 analogs **8–10** with a pentalenofurane scaffold in the ω-side chain.

Funding: The funds were provided by Orizont-2000, 45/1999/1.

Data Availability Statement: Not applicable.

Acknowledgments: We acknowledge the Ministry of Research, Innovation and Digitalization for the grant Orizont-2000, 45/1999/1, and A.H. gratefully acknowledges the University of Bucharest—UniRem project no. 244 and the contract CNFIS-FDI-2020-0355.

Conflicts of Interest: The authors declare no conflict of interest.

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