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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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 C15, cyclopentyl and cyclohexyl scaffolds, etc [1]. In this direction, we previously introduced bicyclo[3.3.0]octene or bicyclo[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.

Figure 1. Prostaglandin analogues with a bicyclo[3.3.0]octene fragment in the ω-side chain and linked to C15 carbon atom

In the first compound, I, the bicyclo[3.3.0]octene fragment is linked to the C16 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 C15 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):

![Diagram of synthesis process](image)

**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 oxidized 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 methane phosphonate 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](image)

**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 methane phosphonate, 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 F₁ 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 (R₁,R₂ = O) (Figure 1), as expected. The Luche reduction of enone 8 with NaBH₄ and CeCl₃ 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 PGF₁ analogs 8–10 with a pentalenofurane scaffold in the ω-side chain.

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