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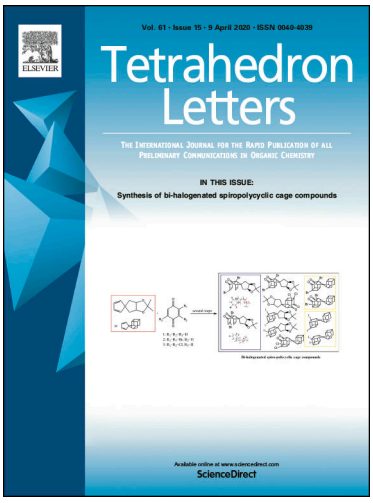

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Synthesis of tetranor-PGE$_1$: a urinary metabolite of prostaglandins E$_1$ and E$_2$

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ABSTRACT

Prostaglandin E$_2$ is produced in response to inflammation, often associated with human disease. As prostaglandins are rapidly metabolized, quantification of end urinary metabolites depend on chemical synthesis of isotopically labeled standards to support metabolite quantification. A concise synthesis of tetranor-PGE$_1$ is described including a late stage incorporation of an isotopically labeled side-chain.

Prostaglandins are key lipid mediators produced as an inflammatory response to potentially harmful stimuli and serve as a hallmark of many human diseases including cancer [1]. Due to their rapid metabolism, detection of prostaglandins, such as PGE$_2$, is not useful as a diagnostic tool but instead detection and quantification of downstream metabolites is useful for prostaglandin analysis (Figure 1) [2]. Metabolic degradation and inactivation of PGE$_2$ commonly starts with enzymatic oxidation by 15-hydroxy-prostaglandin dehydrogenase (15-PGDH) followed by double bond reduction by 15-keto-prostaglandin Δ_{13}-reductase to afford 13,14-dihydro-15-keto PGE$_2$ (Figure 1) [3]. While the keto metabolite is detectable in plasma, it has proven unreliable as a biomarker of PGE$_2$ levels as it has a short half-life ($t_{1/2}$ ~8 min) and subject to further metabolism leading to tetranor-PGEM, a reliable marker of endogenous PGE$_2$ production [4]. PGEM is increased in patients with cystic fibrosis [5], correlates with plasma virus load in HIV [6], and is increased in many types of cancer [7]. A recent meta-analysis concluded that PGEM is the most promising urinary biomarker for colorectal cancer risk assessment and screening [7a]. Thus, accurate assessment of endogenous PGE$_2$ production is essential.

Oates and Samuelsson later identified tetranor-PGE$_1$, a second, albeit minor, urinary metabolite [2b]. In this case the aforementioned oxidation-reduction of the ω-side-chain is by-passed and the α-side-chain cleaved by enzymatic β-oxidation (Figure 1). In support of a proposed clinical study we required a chemical synthesis of tetranor-PGE$_1$ and a deuterium labeled derivative for its quantification in human urine.

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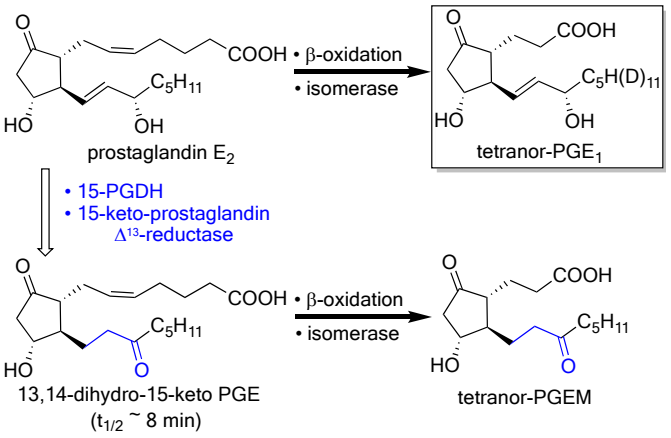


Figure 1. Two metabolic pathways of prostaglandins E$_2$ leading to tetranor-PGE$_1$ and tetranor-PGEM.

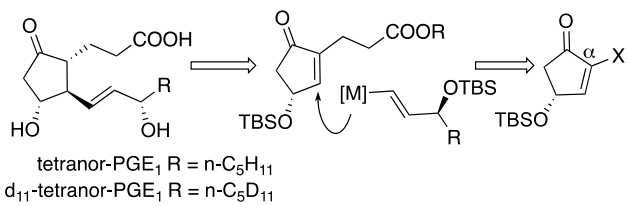
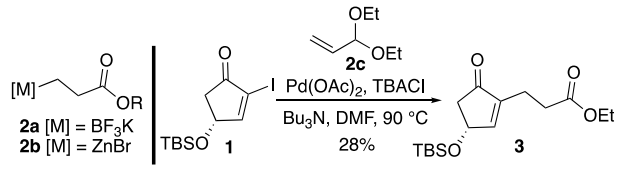


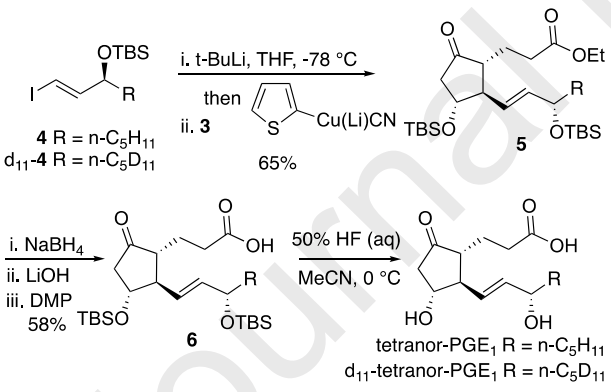
Figure 2. Two-component coupling synthetic strategy.

been extensively studied since the 1960's [8]. Among the synthetic strategies developed, the two-component (conjugate addition) coupling process suited our needs as the starting materials are easily available and introduction of an isotopically labeled side-chain would be conveniently introduced late in the synthesis (Figure 2). Key to our approach was α-functionalization of iodoenone **1** by a cross-coupling reaction, a strategy popularized by Johnson and co-workers [9].



Scheme 1. Cross-coupling partners examined and successful Heck coupling with iodoenone **1**.

We started our synthetic investigations by examining the cross-coupling of iodoenone **1** with metal homoenolates (Scheme 1). Iodoenone **1** was conveniently prepared in high optical purity following established procedures starting from cyclopentadiene [9,10]. As B-Alkyl Suzuki cross-coupling of iodoenone **1** has been employed en route to prostaglandins and analogues we first examined potassium trifluoroborate **2a** as a coupling partner [11]. Unfortunately under reaction conditions used previously to couple with aryl halides we only observed starting material and decomposition. Similar results were obtained when employing zinc homoenolate **2b** in a Negishi coupling reaction. Fortunately Heck coupling with acrolein diethyl acetal **2c** with iodoenone **1** under Jeffries conditions, previously reported using aryl halide coupling partners [12], afforded ester **3** in 28% yield. Although the yield of this reaction was low, it was reproducible and allowed us to proceed toward the synthesis of tetranor PGE_1.



Scheme 2. Synthesis of tetranor-PGE_1 and d_{11}-tetranor-PGE_1.

As anticipated, addition of the mixed higher-order cuprate reagent derived from 3*S*-vinyl iodide **4** to enone **3** afforded cyclopentanone **5** with expected trans, trans diastereoselectivity [9,13]. Vinyl iodide **4** (R = n-C_5H_{11}) was prepared following well-established synthetic methods employing an asymmetric Noyori reduction of an intermediate alkynone derived from alkynylation of hexanoyl chloride [14]. Deuterium labeled d_{11}-**4** was prepared from d_{11}-hexanoyl chloride derived from commercial d_{11}-hexanoic acid. Saponification of ester **5** proved problematic due to facile beta-elimination of the TBS ether within the cyclopentanone core. The elimination problem was circumvented using a three-step procedure (**5** to **6**) reported by Taber as he encountered the same problem in his synthesis of the prostaglandin metabolite PGE_2U_M [15]. Treatment of carboxylic acid **6** with aqueous HF in acetonitrile afforded tetranor-PGE_1. ergo decomposition and was therefore kept as a solution in ethyl acetate. The utility d_{11}-tetranor-PGE_1 of the latter in quantifying tetranor-PGE_1 in clinical urine samples will be reported in due course.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at do:XXXXX.

Highlights

- Chemi
"tetranor PGE1"
- Heck coupling with acrolein diethyl acetal leads to an ester
- Cuprate conjugate addition to a 2-substited-5-alkoxycylopentenone
- Deuterium labeling affords a standard for a prostaglandin urinary metabolite