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Total Synthesis of Prostaglandin 15d-PGJ$_2$ and Investigation of its Effect on the Secretion of IL-6 and IL-12

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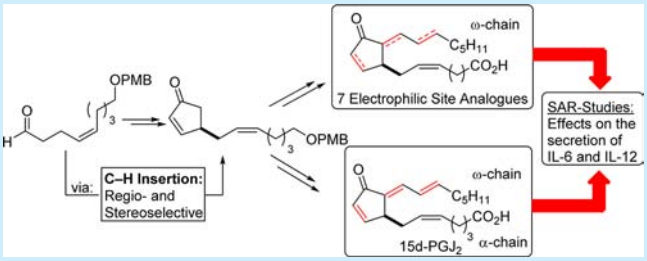
Supporting Information

ABSTRACT: An efficient synthesis of 15-deoxy-Δ12,14-prostaglandin J$_2$ (15d-PGJ$_2$, **1**) is reported. The route described allows for diversification of the parent structure to prepare seven analogues of **1** in which the positioning of electrophilic sites is varied. These analogues were tested in SAR studies for their ability to reduce the secretion of proinflammatory cytokines. It was shown that the endocyclic enone is crucial for the bioactivity investigated and that the conjugated ω-side chain serves in a reinforcing manner.



15-Deoxy-Δ12,14-prostaglandin J$_2$ (15d-PGJ$_2$, **1**) is a recently described prostanoid eicosanoid receiving considerable attention as a consequence of its extraordinary biological activity in the modulation of inflammatory and apoptotic processes.[1] While the majority of the other prostaglandins act in a proinflammatory fashion, 15d-PGJ$_2$ (**1**) was recognized for its contrary effects and is therefore referred to as "the anti-inflammatory prostaglandin".[1a] Cyclopentenone prostaglandins such as 15d-PGJ$_2$ (**1**) differ from the other prostaglandins not only in their biological mode of action, but also in their structural properties.[2] Prostaglandin **1**, for instance, contains a cross-conjugated trienone and therefore has become an attractive synthetic target that has been the subject of four total syntheses prior to this work.[3] Recently, we have established an efficient synthetic route to the structurally similar cyclopentenone epoxyisoprostanes EC (**2**) and EI (**3**) and have investigated their role in inhibiting secretion of proinflammatory cytokines IL-6 and IL-12.[4] Compounds **2** and **3** differ from 15d-PGJ$_2$ (**1**) by the presence of an allylic epoxide and the disposition of the carboxylic acid (Figure 1). Herein,

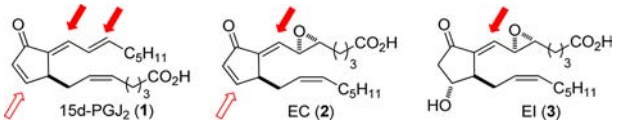


Figure 1. Structures of 15d-PGJ$_2$ (**1**), EC (**2**), and EI (**3**).

we implement a modification of our approach to EC (**2**) toward the synthesis of **1**, enabling the preparation of a collection of seven enone analogues (Figure 2). Biological testing of the analogue structures disclosed that for 15d-PGJ$_2$ (**1**) the endocyclic enone is of critical importance. Furthermore, we could show that the 1,6-dienone in the ω-side chain acts

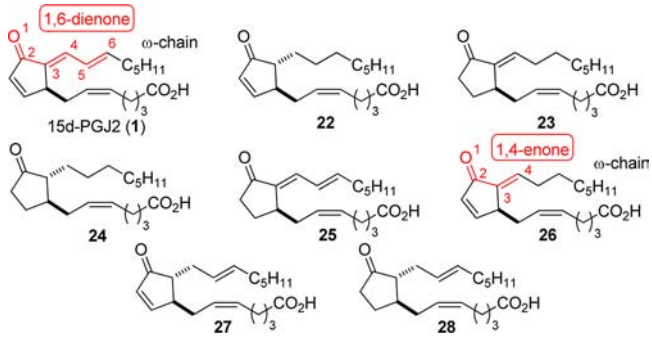


Figure 2. 15d-PGJ$_2$ (**1**) and analogues **22**–**28** with varying double-bond pattern. The 1,6-dienone in **1** and 1,4-enone in **26** are highlighted in red.

deactivating compared to the analogue 1,4-enone that was identified as the more potent compound (Figure 2, **1** vs **26**). The two distinct enone systems are highlighted in red in compounds **1** and **26** in Figure 2.

In previous work, we have shown that the potency of the epoxyisoprostanes **2** and **3** is higher than that of 15d-PGJ$_2$ (**1**) and that the lactone resulting from epoxide opening by the carboxylic acid in EC (**2**) affords a highly potent anti-inflammatory agent.[5] Furthermore, we demonstrated that the endocyclic enone (indicated by ⇨ in Figure 1) is crucial for bioactivity and that **3** is most probably a precursor of **2**.[5] Prostaglandin **1** also incorporates an endocyclic enone but shows much lower potency. The difference in the positioning of the carboxylic acid in **1** versus **2** and **3** suggests that the inability to form a γ-lactone as observed for the latter two could be

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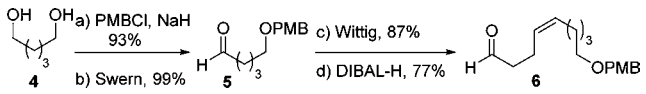
responsible for its distinct activity. Additionally, we wondered whether the variations in biological activity could be derived from differences in the nature of the electrophilic sites (indicated by ➡ in Figure 1). To test this hypothesis, we synthesized 15d-PGJ_2 (**1**) and its analogues varying in the positioning of the double bond.

The synthetic endeavors commenced with preparation of a precursor enabling installation of the α-chain, namely aldehyde **6**. It was prepared employing a four-step synthetic sequence, as shown in Scheme 1. 1,5-Pentanediol **4** was protected as the

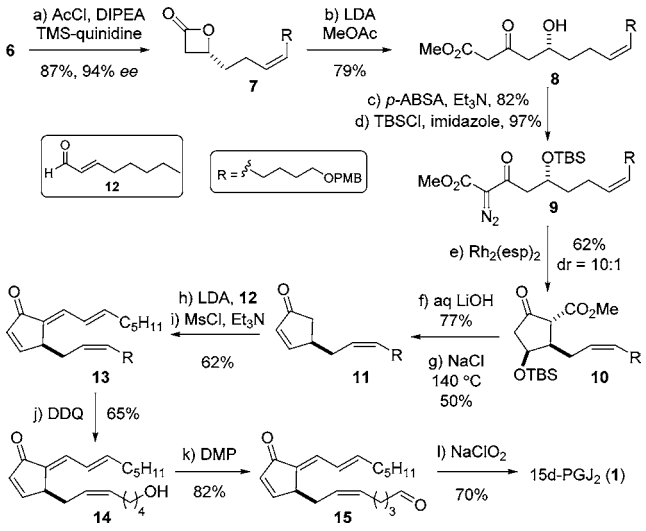
Scheme 1. Synthesis of the α-Chain Aldehyde 6



corresponding PMB-ether and the remaining alcohol subjected to oxidation employing Swern conditions to yield aldehyde **5**. Wittig olefination of the aldehyde with the phosphonium salt generated from ethyl 4-bromobutanoate and PPh_3 exlusively gave a (*Z*)-olefin. Selective reduction of the ethyl ester to aldehyde **6** was accomplished using 1 equiv of DIBAL-H in toluene at −78 °C to furnish **6**.

Treatment of **6** with ketene as described by Nelson afforded **7** in 87% yield and 94% ee (Scheme 2).[6] β-Lactone **7** was

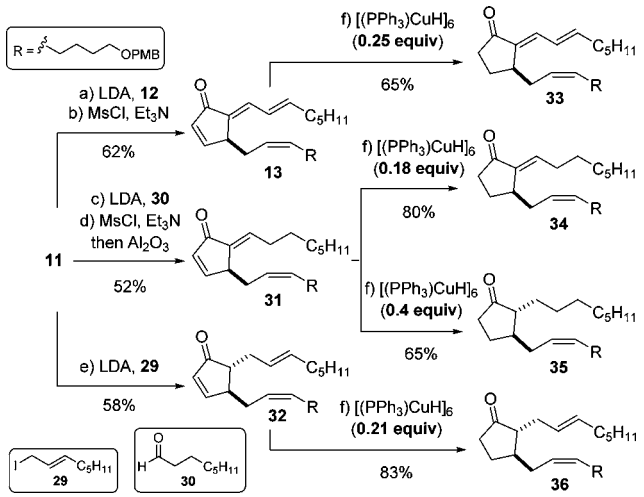
Scheme 2. Synthesis of 15d-PGJ_2 (1)



subjected to ring opening to give β-keto-δ-hydroxy ester **8**, which after diazotization and protection yielded **9**. Cyclization of **9** through a C−H insertion reaction ($Rh_2(esp)_2$) furnished cyclopentanone **10** in 62% yield and high diastereoselectivity (10:1) as determined by ^{1}H NMR spectroscopy. Heating of **10** in the presence of LiOH in THF/water at reflux led to an α,β-enone. Subsequent decarboxylation under Krapcho conditions afforded cyclopentenone **11**, an intermediate of a previous synthesis of 15d-PGJ_2 (**1**) by Kobayashi and Acharya.[3c,d] The ω-side chain was installed through the implementation of a stepwise aldol condensation reaction with aldehyde **12** to obtain PMB ether **13**. Deprotection of the PMB ether (**13** → **14**) and stepwise oxidation of the alcohol to the acid furnished 15d-PGJ_2 (**1**). To assess the nature of the electrophilic sites in **1** crucial for inhibition of proinflammatory IL-6 and IL-12 secretion, we synthesized all seven possible electrophilic site analogues **22**−**28** (Figure 2).

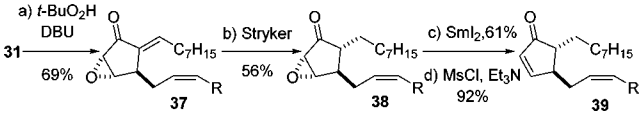
The synthesis of analogues **22**−**28** commenced with cyclopentenone **11**. The ω-side chain was installed either by aldol condensation or alkylation reactions, depending on the requisite double-bond pattern in the targeted molecule (Scheme 3). Trienone **13** was prepared as described before

Scheme 3. Divergent Synthesis of the Precursors 13, and 31−36 from 11



for the synthesis of 15d-PGJ_2 (**1**, Scheme 2). Dienone **31** was accessible by an aldol condensation reaction employing octanal (**30**) as reaction partner. In contrast to the preparation of **13**, the elimination step required the addition of neutral Al_2O_3. In the presence of HMPA as a cosolvent, alkylation of enolized cyclopentenone **11** with allylic iodide **29** could be achieved.[7] Enones **13**, **31**, and **32** not only served as precursors for **1** and the analogues **26** and **27** (Figure 2), but were also further elaborated into precursors **33**−**36** by treatment with Stryker's reagent (Scheme 3).[8] Alterations in the stoichiometry of this reagent allowed for selective enone reductions.[5] Direct alkylation of cyclopentenone **11** with 1-iodooctane to give the precursor for analogue **22** with the saturated ω-chain was met with failure under a variety of conditions. Therefore, for the preparation of precursor **39** (Scheme 4), a strategy was

Scheme 4. Preparation of Analogue Precursor 39



chosen in which the endocyclic enone was temporarily masked.[5] Epoxidation of the more reactive endocyclic enone afforded epoxide **37**. Treatment with Stryker's reagent furnished epoxide **38**, which upon reductive epoxide opening and elimination of the β-hydroxy group regenerated the endocyclic enone to yield precursor **39**.[9]

With the precursors in hand, adjustment of the oxidation state of the masked primary alcohol (Scheme 5) remained for completion of the synthesis of the targeted 15d-PGJ_2 analogue structures **22**−**28**. Cleavage of the PMB ethers and two-step oxidation of the resulting primary alcohols to the carboxylic acids provided **22**−**28**.

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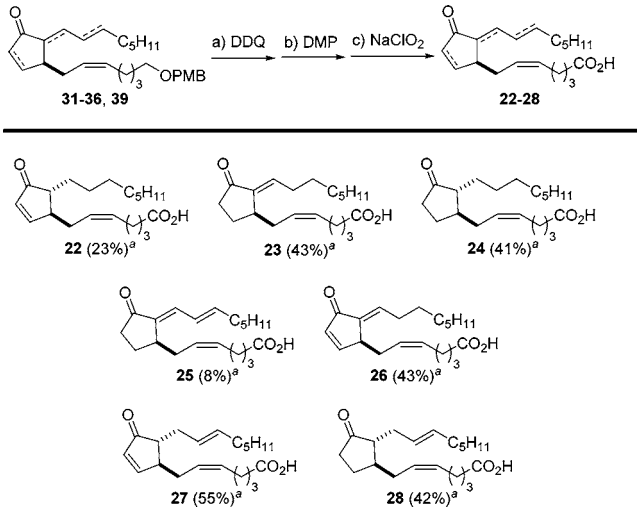
Scheme 5. Preparation 15d-PGJ$_2$-Analogues 22−28



[a]Combined yields over three steps.

Analogues **22−28** were tested together with parent 15d-PGJ$_2$ (**1**) for their ability to reduce IL-6 and IL-12 secretion in bone marrow-derived dendritic cells (BMDCs, Figure 3). All

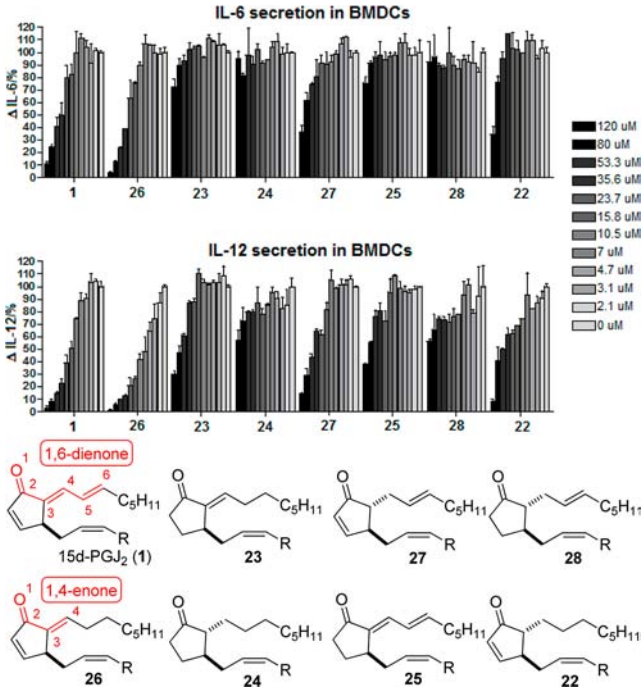


Figure 3. Biological testing of 15d-PGJ$_2$ (**1**) and its analogues **22−28** for their ability to reduce the secretion of proinflammatory cytokines IL-6 and IL-12. R = $C_3H_6CO_2H$.

analogues were less potent than the parent 15d-PGJ$_2$ (**1**) with the exception of compound **26**. Interestingly, dienone **26** shows higher potency than the parent compound, which indicates that the 1,6-dienone in the ω-side chain of 15d-PGJ$_2$ (**1**) has a less activating effect on the endocyclic enone than the corresponding 1,4-enone in analogue **26**. In this series of analogues, it becomes clear that the endocyclic enone is crucial for bioactivity as the analogues **23**, **24**, **25**, and **28**, all lacking the endocyclic enone, show no effects in reducing IL-6 and IL-12 secretion. Therefore, when the endocyclic enone is absent, the biological activity investigated in this context is completely lost. Analogues that contain the endocyclic enone but lack additional activation by conjugation to the ω-side chain (**27** and **22**) still maintain detectable bioactivity, although they show a marked decrease.

In summary, we have demonstrated the application of a synthetic route previously developed for the synthesis of epoxyisoprostanes EC (**2**) and EI (**3**)[4] to the preparation of structurally related prostaglandin 15d-PGJ$_2$ (**1**). Cyclopentenone **11** served as a key intermediate that enabled the preparation of seven analogue structures of **1** that vary in their disposition of electrophilic sites. With these analogues in hand we could identify the endocyclic enone as critical for the activity of 15d-PGJ$_2$ (**1**) as inhibitor for the secretion of proinflammatory IL-6 and IL-12. Finally, cross-conjugation in the ω-side chain of the parent prostanoid enhances the electrophilic properties of the endocyclic enone, and this effect is enhanced for the structure encompassing a 1,4-enone in the ω-side chain in lieu of a 1,6-dienone, a feature which renders analogue **26** a more potent compound than parent 15d-PGJ$_2$ (**1**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02181.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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