Communication

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Concise Syntheses of Δ^{12}-Prostaglandin J Natural Products via Stereoretentive Metathesis

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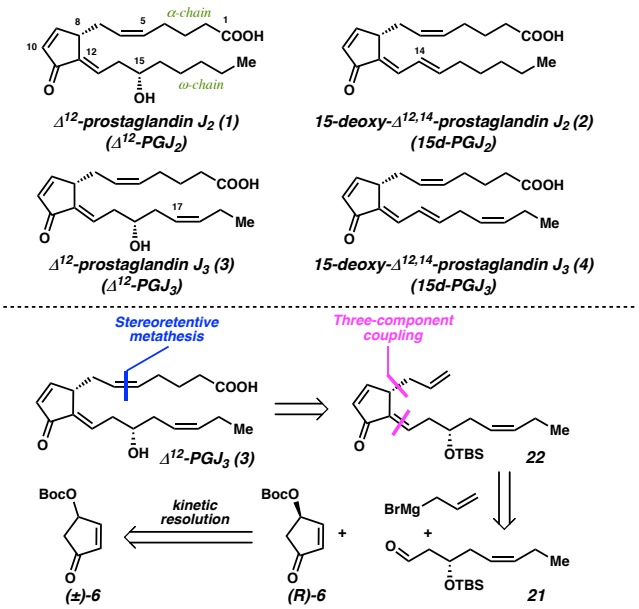
Supporting Information Placeholder

ABSTRACT: Δ^{12}-Prostaglandin J family is recently discovered and has potent anti-cancer activity. Concise syntheses of four Δ^{12}-prostaglandin J natural products (7–8 steps in the longest linear sequences) are reported, enabled by convergent stereoretentive cross-metathesis. Exceptional control of alkene geometry was achieved through stereoretention.

Prostaglandins are an important class of naturally occurring molecules that are found in mammalian tissues and exhibit a broad range of biological functions and widespread medical applications.[1] Efforts directed toward the synthesis of various prostaglandins has had a profound effect on the development of new strategies and tactics employed in the field of synthetic chemistry, emanating from the seminal studies of Corey beginning in the 1960's.[2] The recently discovered Δ^{12}-prostaglandin J family (**1**–**4**, Scheme 1) features a unique cross-conjugated dienone motif and appealing anticancer activity.[3] Δ^{12}-PGJ$_3$ (**3**), for example, was isolated as a secondary metabolite and was shown to selectively induce apoptosis of leukemia stem cells over normal hematopoietic stems cells with high potency.[4] Studies of its stability, bioavailability, and hypersensitivity make Δ^{12}-PGJ$_3$ an intriguing drug candidate for leukemia treatment.[5] Synthetic efforts toward Δ^{12}-prostaglandin J compounds began in 2003, with a number of syntheses of Δ^{12}-PGJ$_2$ (**1**) and 15d-PGJ$_2$ (**2**) reported through various approaches.[6] Elegant contributions to the total synthesis of Δ^{12}-PGJ$_3$ (**3**) were reported by Nicolaou and co-workers[7] and more recently by the Aggarwal group.[8] A number of Δ^{12}-PGJ$_3$ analogues were also accessible via a streamlined synthesis developed by Nicolaou and co-workers[9] to enable a comprehensive structural-activity relationship (SAR) study of their anti-cancer activities.

Olefin cross-metathesis is a convergent method for building C–C double bonds in natural product syntheses;[10] however, it has seldom been applied in the previous syntheses of Δ^{12}-PGJ family. Most importantly, conventional metathesis catalysts typically gave imperfect control of alkene geometry. Previous syntheses relied on the semi-hydrogenation of alkynes or Wittig reactions, requiring multi-step functional group manipulation with concomitant waste generation. From a strategic perspective, chemoselectivity among multiple alkenes has also been another concern, especially in the later stages. Stereoselective and alkene-chemoselective metathesis catalysts are in demand to realize a convergent synthesis from simple alkene building blocks.

Scheme 1. Δ^{12}-Prostaglandin J Natural Products and Retrosynthetic Analysis



A series of cyclometallated ruthenium-based catalysts (e.g. **Ru-1**, **Ru-2**, Figure 1) were recently developed by Grubbs and co-workers, [11] and enabled *Z*-selective metathesis through a favored *syn*-metallacyclobutane intermediate (Figure 1, Path A). More recently, catechodithiolate-based catalyst **Ru-3** and its dithiolate variants were developed by Hoveyda group and showed high *Z*-selectivity in ring-opening metathesis polymerizations, ring-opening cross-metathesis, and cross-metathesis with *Z*-olefins.[12] In fact, high kinetic *E*-selectivity in cross-metathesis with *E*-starting materials was also observed with **Ru-3**, the sIPr analogue **Ru-4,** and other less bulky fast-initiating analogues developed by Materia Inc. and the Grubbs group,[13] that defined these catalysts as stereoretentive. The origin of the stereoretention

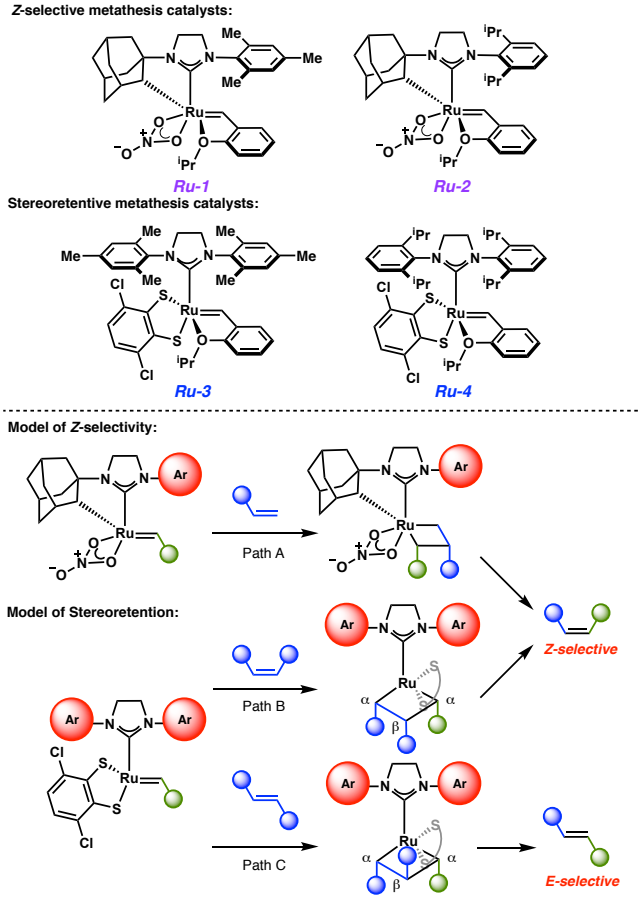


Figure 1. *Z*-selective and Stereoretentive Metathesis Catalysts and Models of Their Stereoselectivity

was attributed to the formation of a side-bound metallacyclobutane intermediate, of which the α-substituents are forced down to minimize steric interactions with the bulky *N*-aryl groups of the NHC. As a result, when starting with *Z*-alkenes, the β-substituent points down to generate *Z*-alkene products (Figure 1, Path B). When starting with *E*-alkenes, however, the β-substituent has to point up into the open space between two *N*-aryl groups, leading to the generation of *E*-alkene products, albeit with slower rates (Figure 1, Path C). Cross-metathesis between two terminal alkenes is not possible with stereoretentive metathesis catalysts, however, because the intermediate methylidene species are unstable and lead to catalyst decomposition.[12d] A methylene capping strategy was recently reported as a remedy to this problem, enabling the cross-metathesis of two terminal alkenes.[14]

Despite the unique properties of these stereoretentive catalysts, to date, limited synthetic evaluation of these catalysts has been conducted.[15] Herein, we present a total synthesis of the olefin-enriched Δ^{12}-prostaglandin J natural products **1**–**4** by implementing a concise stereoretentive metathesis approach. This also sets a perfect test ground to evaluate the reactivity, chemoselectivity, and functional group compatibility of these newly developed metathesis catalysts.

Retrosynthetically, Δ^{12}-PGJ$_3$ (**3**) for example can be simplified into a truncated prostaglandin structure **22** by use of stereoretentive metathesis (Scheme 1). A three-component coupling strategy[16] can be applied toward the synthesis of **22**, using a relatively simple and commercially available allyl Grignard reagent, ω-chain aldehyde **21**, and a chiral cyclopentenone (***R*)-6**. The O-Boc group of (***R*)-6** can be used as a traceless stereoinductive group to set the C8 stereocenter.[17]

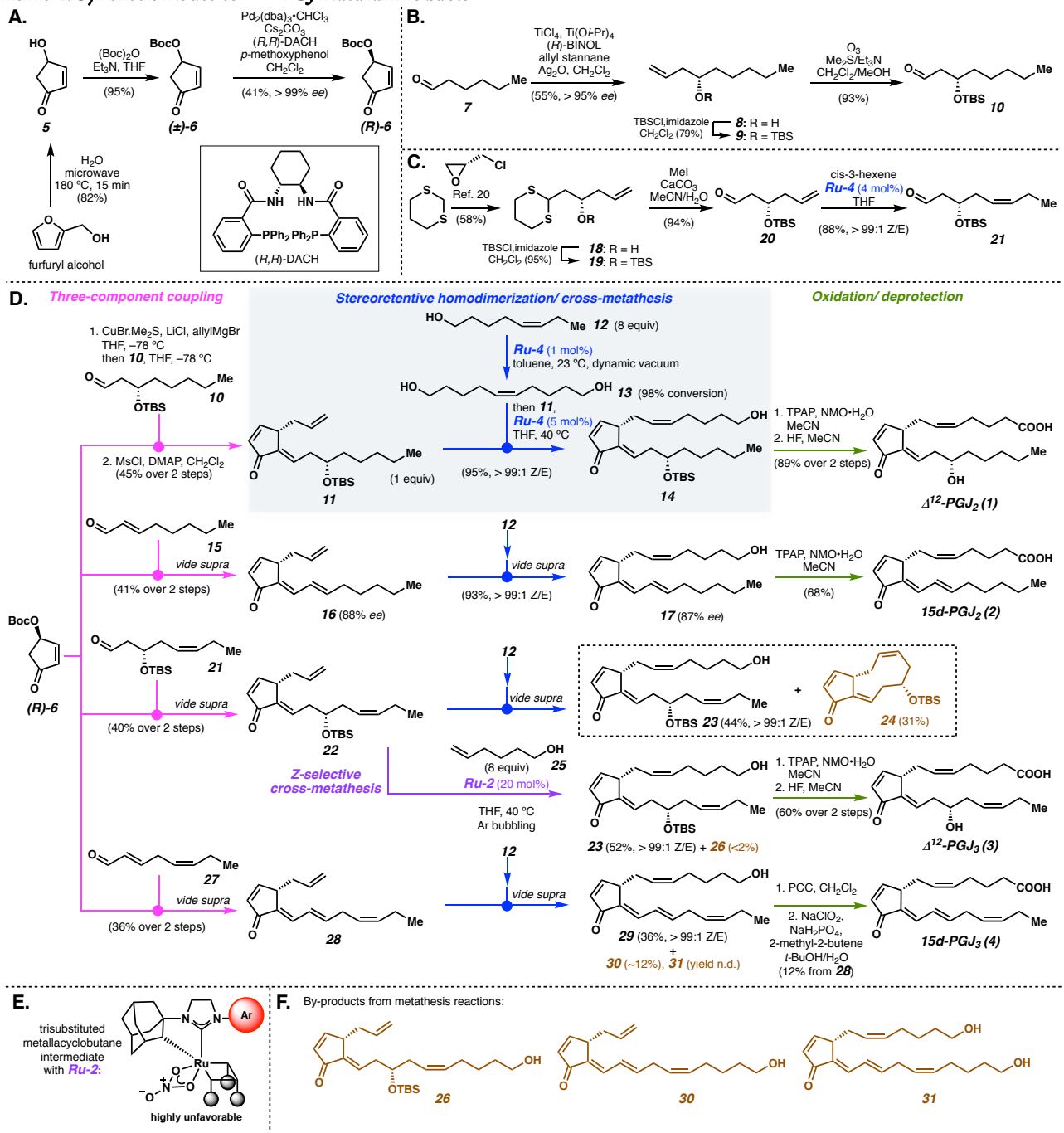
We initially aimed to synthesize Δ^{12}-PGJ$_2$ (**1**). Chiral cyclopentenone (***R*)-6** was prepared from furfuryl alcohol in a three-step process including a kinetic resolution method developed by Reiser and coworkers (Scheme 2A).[18] The ω-chain aldehyde **10** was prepared from hexanal (**7**) through asymmetric Keck allylation,[19] TBS protection, and ozonolysis (Scheme 2B). With all the starting materials for the three-component coupling in hand, CuBr•Me$_2$S and LiCl facilitated the diastereoselective conjugate addition of the allyl magnesium bromide. The enolate formed can then be trapped by the subsequently added ω-chain aldehyde electrophile, and the O-Boc group was eliminated in the course of the aldol reaction to form the desired cyclopentenone. Elimination with MsCl and DMAP favored 12*E*-product **11** as the major product in reasonable yield (45% over 2 steps, Scheme 2D).

Stereoretentive metathesis was then evaluated on **11**. Since **11** cannot react with another terminal alkene using stereoretentive metathesis catalysts, we considered a symmetric *Z*-alkene **13** as the coupling partner, which could also be made by homodimerization of readily available **12** through stereoretentive metathesis. With 1 mol% loading of **Ru-4** as the catalyst, 98% conversion could be achieved by applying dynamic vacuum to remove the by-product, *cis*-3-hexene (bp 66–68 °C) from the reaction mixture. Next, **11** with an additional 5 mol% catalyst **Ru-4** were added into the reaction mixture, and the alcohol product **14** could be isolated in 95% yield in high *Z*-selectivity (>99% *Z*). This result established the efficacy of an efficient one-pot, stereoretentive homodimerization/cross-metathesis strategy to build the C5 *Z*-alkene. In contrast, synthesis of PGE$_2$ and PGF$_{2\alpha}$ required a large excess of gaseous butene and more complicated operations in the previously reported methylene capping strategy.[14] Ley oxidation and deprotection of the TBS group of **14** in aqueous HF furnished the natural product Δ^{12}-prostaglandin J$_2$ (**1**) in 89% yield over the last two steps.

The same three-component coupling sequence was performed to obtain **16**, and the enal functionality of aldehyde **15** was well tolerated in the aldol step. **16** was then subjected to the standard one-pot stereoretentive homodimerization/cross-metathesis conditions, and alcohol **17** was obtained in excellent yield (93% yield, Scheme 2D) with high *Z*-selectivity (>99% *Z*). The C14 *E*-alkene tolerated the reaction, consistent with the much slower reaction of *E*-alkenes with **Ru-4** as seen previously.[13] We also assessed the enantiopurity of intermediates **16** and **17**. Three-component coupling product **16** proceeded with a small loss in enantiopurity (88% *ee*) from (***R*)-6** (>99% *ee*), but the metathesis product **17** was obtained without significant erosion of enantiopurity (87% *ee*). This result demonstrates that stereoretentive metathesis with catalyst **Ru-4** also retained the stereochemistry of the C8 stereocenter. Ley oxidation of **17** again gave 15-deoxy-$\Delta^{12,14}$-prostaglandin J$_2$ (**2**) in 68% yield.

Synthesis of Δ^{12}-prostaglandin J$_3$ (**3**) began with the preparation of the ω-chain aldehyde **21**. We envisioned the *Z*-alkene in **21** could also be generated from stereoretentive metathesis. First, we obtained chiral alcohol **18** through a

Scheme 2. Synthetic Route to Δ^{12}-PGJ Natural Products



reported chiral pool strategy with (*R*)-epichlorohydrin as the starting material (Scheme 2C).[20] TBS protection of the alcohol and subsequent removal of the 1,3-dithiol gave aldehyde **20**. Stereoretentive metathesis of **20** with an excess amount of *cis*-3-hexene using catalyst **Ru-4** (4 mol%) afforded ω-chain aldehyde **21** in good yield (88%) with high *Z*-selectivity (>99% *Z*). The short synthesis of aldehyde **21** proved that a broad range of functional groups, including aldehydes, can be tolerated without protecting group manipulations using stereoretentive catalysts. Then, **22** was synthesized through the standard three-component coupling sequence from **(*R*)-6** (Scheme 2D). Surprisingly, fast ring-closing metathesis (RCM) with **Ru-4** yielded **24** as a by-product (31% yield) bearing an unusual 9-membered ring, and the desired alcohol product **23** was obtained in only 44% yield.

Alternatively, we chose to use cyclometallated catalyst **Ru-2** to circumvent the crossover of alkene reactivity. Because tri-substituted metallacyclobutane intermediates are highly unfavorable with this cyclometallated catalyst, this pathway can be easily avoided (Scheme 2E).[21] Chemoselective cross-metathesis of 5-hexen-1-ol (**25**) with the allyl group of **22** furnished the desired product **23** in good yield (52%) with a trace amount of by-product **26** (less than 2%, Scheme 2F). The RCM product **24** was not observed under these conditions. The side-reaction of C17 internal *Z*-alkene could be attributed to ethylene produced or the residual ruthenium methylidene species in the solution. Then, Ley oxidation of

23 and deprotection of the TBS group with aqueous HF provided Δ^{12}-prostaglandin J_3 (**3**) in 8 linear steps.

Finally, in the synthesis of 15d-PGJ_3 (**4**), crossover of metathesis reactivity between the allyl group and the C17 *Z*-alkene of **28** could also be expected. Standard stereoretentive metathesis conditions with **Ru-4** provided desired product **29** in 36% yield and by-products **30** and **31** (Scheme 2F).[22] Compared to Δ^{12}-PGJ_3 (**3**) synthesis, where the steric bulk of the OTBS group may be beneficial to achieving good chemoselectivity, **28** has no such steric hindrance. However, no RCM of **28** was observed, possibly due to the ring strain of RCM product. Though **30** could not be separated from **29**, the mixture was subjected to PCC oxidation and Pinnick oxidation conditions[23], allowing us to isolate 15-deoxy-$\Delta^{12,14}$-prostaglandin J_3 (**4**) (12% yield from **28**).

In conclusion, we report a concise and convergent synthesis of four Δ^{12}-prostaglandin J natural products in shorter sequences (7–8 steps in the longest linear sequences) empowered by stereoretentive and stereoselective metathesis. Furthermore, the reactivity, chemoselectivity, and functional group compatibility of stereoretentive metathesis was evaluated. This study should inspire further practical applications of stereoselective metathesis, such as a facile one-pot stereoretentive homodimerization/cross-metathesis strategy to introduce *Z*-alkenes with excellent geometric control. The modularity and expediency of this chemistry opens the synthesis of other prostaglandins and analogues to enable SAR studies in cancer treatment. With the well-defined kinetically *Z*/*E*-selective catalysts that have been developed to overcome the inherent thermodynamic preference of alkene product geometry, olefin metathesis can play a pivotal role in the synthesis design.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.xxxxxxx. Characterization data, and experimental data (PDF)

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Notes

The authors declare no competing financial interest.

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Dedicated to Professor E. J. Corey on the occasion of his 90th birthday.

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(22) **28** as well as by-products **29, 30** was obtained using **Ru-2** and no improvement of chemoselectivity was observed (see Supporting Information).

(23) Ley oxidation of a mixture of **29** and **30** was also performed but resulted in a significant amount of decomposition products.

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