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The First Total Synthesis of 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 and the Unambiguous Assignment of the C^{14} Stereochemistry

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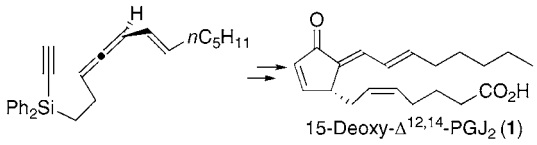
ABSTRACT



The first total synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 is reported. The highly unsaturated cyclopentenone prostaglandin was obtained via a silicon-tethered allenic [2 + 2 + 1] cycloaddition reaction developed in our group. In addition, the stereochemistry at C^{14} has been assigned unambiguously.

Cyclopentenone prostaglandins have emerged in the past decade as uniquely different from other compounds in the prostaglandin family.[1] These highly unsaturated prostaglandins have antineoplastic, antiinflammatory, and antiviral activities and elicit a biological response, not by binding to G-protein-coupled receptors, but instead by interacting with cellular targets, including signaling molecules and transcription factors.[2] For example, 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**1**) represents the highest affinity natural ligand identified to date for PPARγ, a receptor that has been linked to type II diabetes, obesity, hypertension, and atherschlerosis.[2] New insights into the biological activity and cellular targets of cyclopentenone prostaglandins and the prostaglandin-like clavulones[3] have led to an increased need for synthetic approaches to these compounds.[3,4] Since cyclopentenone prostaglandins are produced in vivo on a need only basis, in very small quantities (<1 mg), their chemical synthesis is a requirement for further research. Approaches to prostaglandins have been described as early as the 1960s, and the literature abounds with syntheses of the various prostaglandins and their analogues.[5] However, the total synthesis of cyclopentenone prostaglandins requires a different approach than has classically been used for their more saturated counterparts since they are typically obtained using dehydration protocols that often lead to mixtures of isomers. Interestingly, it is this mixture of isomers that has led to some ambiguity involving the stereochemistry of 15-deoxy-$\Delta^{12,14}$-PGJ_2 (vide infra).[6]

A more direct strategy for the synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**1**) incorporates an allenic Pauson−Khand-type reaction since access to α-alkylidene and 4-alkylidene cyclopentenones via this protocol has proven to be efficient and general.[7] Thus, direct access to the α-alkylidene core of **1** might involve an intermolecular reaction between an appropriately functionalized allene and acetylene gas. Unfor-

(1) For a review, see: Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185.

(2) Wahli, W.; Braissant, O.; Desvergne, B. *Chem. Biol.* **1995**, *2*, 261. Forman, B. M.; Tontonoz, P.; Chen, J.; Brun, R. P.; Spiegelman, B. M.; Evans, R. M. *Cell* **1995**, *83*, 803.

(3) (a) Ciufolini, M. A.; Zhu, S. *J. Org. Chem.* **1998**, *63*, 1668. (b) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219.

(4) For more selected synthetic approaches to cross-conjugated cyclopentenones, see: Kobayashi, Y.; Murugesh, M. G.; Nakano, M. *Tetrahedron Lett.* **2001**, *42*, 1703. Zhu, J.; Yang, J.-Y.; Klunder, A. J. H.; Liu, Z.-Y.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5847; Liu, Z.-Y.; Dong, H.; Chu, X.-J. *Tetrahedron* **1994**, *50*, 12337. Hashimoto, S.; Arai, Y.; Hamanaka, N. *Tetrahedron Lett.* **1985**, *26*, 2679.

(5) *Advances in Prostaglandin, Thromboxane, Leukotriene Research*; Raven: New York, 1983−1991; Vols. 11−21.

(6) Maxey, K. M.; Hessler, E.; MacDonald, J.; Hitchingham. L. *Prostaglandins Other Lipid Mediators* **2000**, *62*, 15−21.

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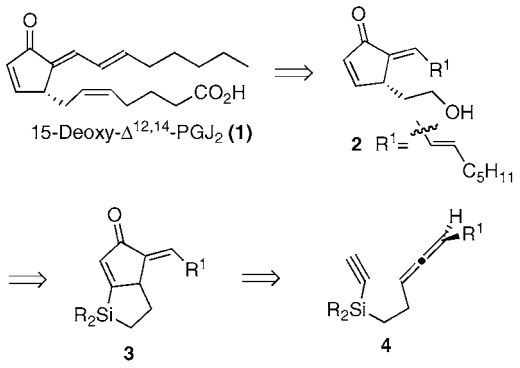
tunately, this process is not well-behaved and typically mixtures of products are obtained in moderate yields favoring the formation of the 4-alkylidene cyclopentenones.[8] However, taking advantage of a removable tether allowed the target ring system to be obtained intramolecularly. Along these lines, we recently reported a successful silicon-tethered allenic Pauson−Khand reaction and felt that this protocol was ideally suited for the total synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2.[9]

Retrosynthetically, it was envisioned that 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**1**) could be obtained from cyclopentenone **2** via an oxidation of the primary hydroxyl group, followed by a well-precedented Wittig reaction on the resulting aldehyde (Scheme 1). In turn, the appending hydroxyl group is the

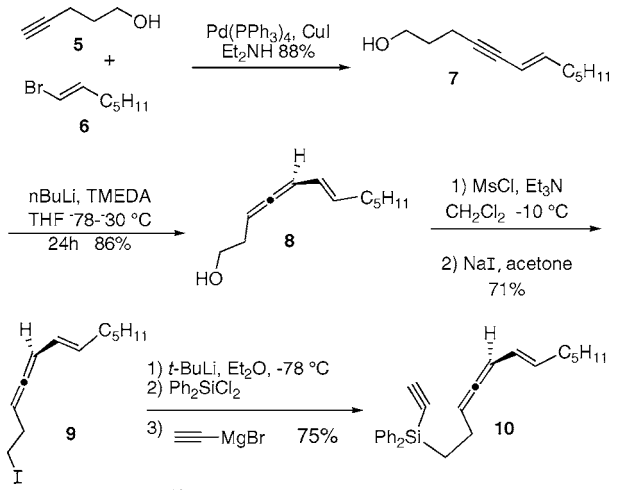
Scheme 1. Retrosynthetic Analysis



product of a selective cleavage of the vinyl silane of **3**, followed by a Tamao−Fleming oxidation of the intermediate silanol. The bicyclic cyclopentenone **3** can in turn be prepared using an allenic [2 + 2 + 1] cycloaddition reaction. The advantages to this carbon−carbon bond-forming strategy are (1) the controlled and stereoselective introduction of each of the double bonds of 15-deoxy-$\Delta^{12,14}$-PGJ_2 and (2) the ease in which the Pauson−Khand cyclization precursor **4** can be assembled.

The synthesis was initiated by treating 4-pentynol (**5**) and (*E*)-1-bromo-1-heptene (**6**) with the Sonogashira coupling

Scheme 2. Syntheis of Alkynyl Allene Precursor



reaction vessel).[12]

protocol to give the enyne **7** in 88% yield (Scheme 2).[10] Reaction of enyne **7** with *n*-BuLi and TMEDA gives the allenol **8** in 86% yield.[11] Next, allenol **8** was converted to iodide **9** by way of the mesylate in 71% yield for the two-step conversion. Treatment of iodide **9** with *t*-BuLi at −78 °C, followed by the stepwise addition of diphenyldichlorosilane, and then ethynylmagnesium bromide afforded the alkynyl allene **10** in 75% yield (three steps, one reaction vessel).[12]

Alkynyl allene **10** was subjected to the standard molybdenum-mediated conditions to give enones **3*E*** and **3*Z*** in 38% yield in a 1:2 ratio.[13,7a] Attempts were made to increase the yield of this annulation by using other transition metals, but with limited success.[14] While this represents a lower yield than anticipated on the basis of all of our model studies, the bicyclic compound **3*E*** contains nearly all of the functionality necessary to assemble 15-deoxy-$\Delta^{12,14}$-PGJ_2. Furthermore, we have shown that **3*Z*** can be isomerized quantitatively using photolysis to give a 1:1 mixture of **3*Z*** and **3*E***. Alternatively, complete isomerization of **3*Z*** to **3*E*** has also been effected in 64% yield using boron trifluoride and propanedithiol. Presumably this is a result of an acid-catalyzed addition of the thiol to the β-carbon of the exocyclic double bond followed by bond rotation and elimination. Attempts were not made to optimize these isomerization conditions. The (*E*)-geometry of the C^{14}−C^{15}

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(8) Aumann, R.; Weidenhaupt, H.-J. *Chem. Ber*. **1987**, *120*, 23. Ahmar, M.; Antras, F.; Cazes, B. *Tetrahedron Lett*. **1995**, *36*, 4417. Ahmar, M.; Chabanis, O.; Gauthier, J.; Cazes, B. *Tetrahedron Lett*. **1997**, *38*, 5277. Shibata, T.; Koga, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 911.

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(10) Takahashi, S.; Kuyoyama, Y. Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

(11) Enomoto, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett*. **1986**, *27*, 4599.

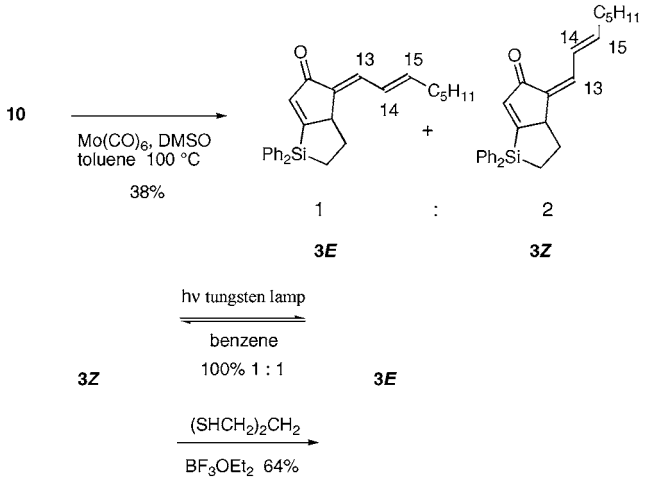
(12) For a procedure to prepare the allenyllithium intermediate, see: Crandall, J. K.; Ayers, T. A. *J. Org. Chem*. **1992**, *57*, 2993.

(13) Jeong, N.; Lee, S. J.; Lee, B. Y.; Chung, Y. K. *Tetrahedron Lett*. **1993**, *34*, 4027.

(14) We found that W(CO)$_5$·THF gave yields nearly identical to that of Mo(CO)$_6$. Interestingly, there was a reversal in the *E*:*Z* selectivity (2:1) when using the tungsten mediator. It was subsequently shown that the stereochemical result was due to an isomerization of the (*Z*)-isomer to the (*E*)-isomer under the reaction conditions. Hoye, T. R.; Suriano, J. A. *Organometallics* **1992**, *11*, 2044.

(15) Prostaglandin numbering system is used.

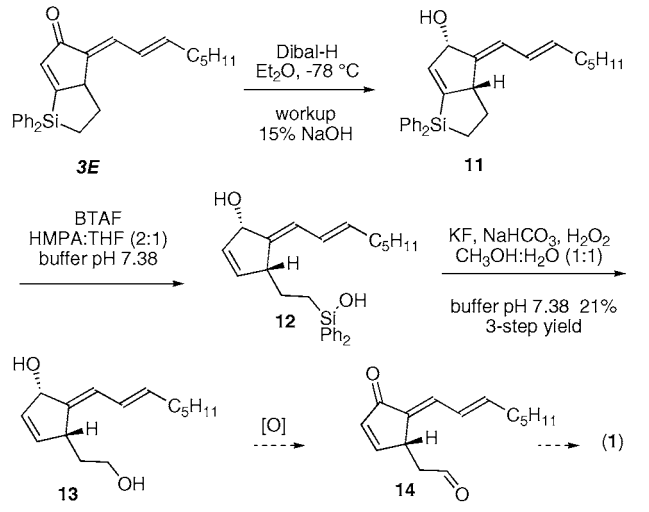
Scheme 3. Allenic [2 + 2 + 1] Cycloaddition



double bond in **3*E*** and **3*Z*** was confirmed by the coupling constants for the olefinic protons on C^{14} and C^{15} ($J = 15.0$ Hz for both compounds).[15] The stereochemistry of the C^{12}–C^{13} double bond was based upon the chemical shift of the olefinic proton on C^{13}, where **3*E*** shows a resonance for H^{13} at δ 6.91 and **3*Z*** shows a resonance for H^{13} at δ 6.45.

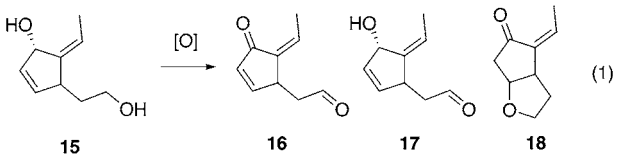
With the (*E*)-alkylidene cyclopentenone **3*E*** in hand, the next step was to cleave the silicon tether (Scheme 4). On

Scheme 4. Synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2



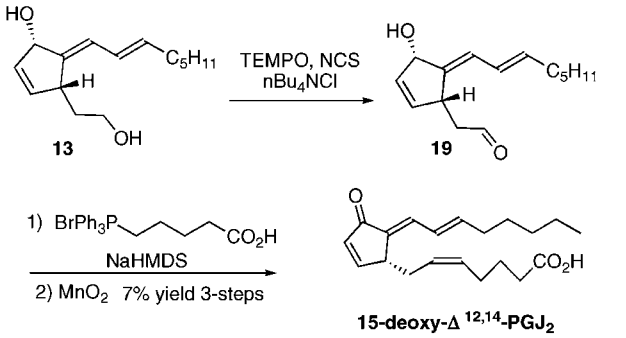
the basis of model studies, moderation of the electrophilicity of the endocyclic double bond of the cyclopentenone **3*E*** was desirable since this olefin appeared to be very reactive toward nucleophiles. Dibal-H reduction at low temperature provided bisallylic alcohol **11**, which proved to be unstable and typically was taken on directly to the next step but could be chromatographed for characterization purposes by pretreating the silica gel with triethylamine. Cleavage of the vinyl silane **11** with benzyltrimethylammonium fluoride using buffered conditions afforded the desired ring-opened product **12** in 70% yield. Silanol **12** was not purified but subjected directly to the Tamao–Fleming oxidation protocol to afford diol **13** in 21% yield over three chemical transformations from **3*E***.[16] Attempts to directly oxidize diol **13** to keto-aldehyde **14** provided complex mixtures of products.

An advanced model system was used to explore various oxidation protocols. Treatment of diol **15** to tetra-*n*-propylammonium peruthenate (TPAP) led to a mixture of products consisting of varying amounts of keto aldehyde **16**, aldehyde **17**, and cyclized Michael adduct **18** (eq 1). Selective oxidation of the allylic alcohol using MnO_2 gave compound **18** in 87% yield, confirming that the primary hydroxyl group adds to initially formed enone.



With this information in hand, it became apparent that it would be necessary to selectively oxidize the primary alcohol in the presence of the secondary alcohol, which was accomplished using the Einhorn protocol to provide aldehyde **19** (Scheme 5).[17] Aldehyde **19** was not purified but reacted

Scheme 5. Completion of Synthesis



with (4-carboxybutyl)triphenylphosphonium bromide[18] and sodium hexamethydisilylamide (NaHMDS) in THF which in turn, upon isolation was immediately oxidized with MnO_2 to provide 15-deoxy-$\Delta^{12,14}$-PGJ_2.

At this time, we believe it necessary to confirm that this is indeed the structure of the natural product. Nearly 20 years after its isolation (by an albumin-catalyzed dehydration of PGD_2)[19] and characterization,[20] a report was published claiming that the stereochemistry at C^{14} of 15-deoxy-$\Delta^{12,14}$-PGJ_2 possessed the (*Z*)- and not the (*E*)-geometry as previously reported.[6] Unfortunately, only HPLC data traces were provided as proof for the authenticity of the C^{14}

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(17) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J. L. *J. Org. Chem.* **1996**, *61*, 7452.
(18) Maryanoff, B. E.; Duhl-Emswiler, B. A. *Tetrahedron Lett.* **1981**, *22*, 4185.

stereochemistry.[21] The proton assignment for each of the resonances in the NMR spectrum (600 MHz) of the synthetic sample are provided in Supporting Information. Particularly noteworthy is the splitting value of 15.0 Hz for H^{14} and H^{15} that corresponds to the (*E*)-isomer. Three discrete samples of 15-deoxy-$\Delta^{12,14}$-PGJ_2 were purchased from Cayman, Inc., and prepared as suggested, and the NMR spectrum was obtained (600 MHz). The spectral data for the samples purchased from Cayman, Inc., completely matched that of the synthetic compound **1**. Moreover, the protons were assigned unambiguously via ^{1}H COSY (600 MHz).

In conclusion, we have completed the first total synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2 using an allenic Pauson−Khand-type reaction to prepare the highly unsaturated α-alkylidene cyclopentenone core. Our approach utilizes a removable silicon tether to set the structure of the monocycle. In addition, we have unambiguously determined that the stereochemistry at C^{14} is *E*, as originally reported in the literature.[22] We are currently applying this synthetic strategy to the stereoselective synthesis of both enantiomers of 15-deoxy-$\Delta^{12,14}$-PGJ_2 and to the synthesis of analogues.

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Supporting Information Available: Characterization data and experimental procedures are provided for compounds **1**, **3*E***, **3*Z***, and **7**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035590V

(19) Bundy, G. L.; Morton, D. R.; Peterson, D. C.; Nishizawa, E. E.; Miller, W. L. *J. Med. Chem.* **1983**, *26*, 790.

(20) Fitzpatrick, F. A.; Wynalda, M. A. *J. Biol. Chem.* **1983**, *258*, 11713. In this report the stereochemistry at C^{14} was depicted as the (*E*)-isomer, but no comment was made with regards to this assignment. Furthermore, the NMR data was obtained on an 80 MHz instrument that showed almost no resolution between H^{10}, H^{14}, and H.[15] Based upon the data at hand, the C^{14} stereochemistry of 15-deoxy-$\Delta^{12,14}$-PGJ_2 was most likely an assumption supported by the albumin-catalyzed dehydration conditions used to access this compound from PGD_2.

(21) NMR spectral data was obtained on a 300 MHz instrument but was not submitted as Supporting Information.

(22) Deoxy-$\Delta^{12,14}$-PGJ_2 has not been isolated from a natural source but has been prepared by an albumin-catalyzed dehydration of PGD_2.