

A → J Prostaglandin Swap: A New Tactic for Cyclopentenone Prostaglandin Synthesis

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Abstract: A practical methodology for the synthesis of J-type prostaglandins has been developed starting from the well-consolidated approaches established for the synthesis of A-type prostaglandins. An efficient 1,3-allylic transposition of the C-9 hydroxyl group of intermediate **4** furnished the advanced precursor **5** for J₂ synthesis. Our optimized A–J swap protocol employed selenium chemistry, involving the [2,3] sigmatropic rearrangement of secondary allylic selenoxide **11a**.

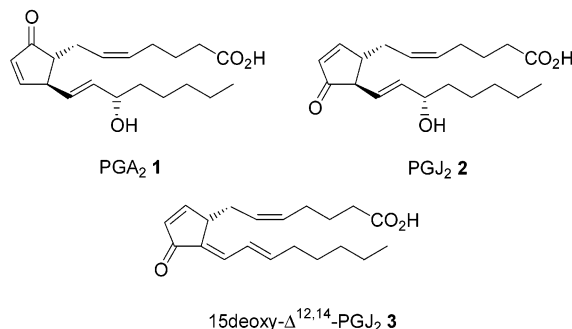
In the past decade there was a renewed interest in prostaglandins of the structurally related A and J classes, in particular in the latter group of cyclopentenone derivatives (Chart 1).¹

Thanks to the progress of molecular biology, a remarkable activity of prostaglandins of the A₂ and J₂ series against a wide variety of DNA and RNA viruses, including HIV-1 and influenza virus, has been proved. These compounds also possess a potent antiinflammatory activity and induce the arrest of cell mitosis at the G₁ phase or the apoptosis of tumor cells, depending on the cell type.² Among the prostaglandins of the A₂ and J₂ series, the latter exert the more powerful activities.³ Indeed, a considerable interest was generated in 1995 by the discovery that 15-deoxy-Δ^{12,14}-PGJ₂ **3** was the natural activating ligand for γ isoform of the peroxisome proliferator-activated receptor (PPARγ). PPARγ is the key regulator of adipocyte differentiation and the molecular target of antidiabetic drugs such as troglitazone and rosiglitazone.⁴ Therefore, prostaglandin **3** is a potent inducer of adipogenesis, promoting differentiation of preadipocytes into mature triglyceride-containing fat cells.

Surprisingly, despite the impressive number of reports regarding the biological activities of J₂ prostaglandins, less attention was paid to their synthesis.⁵

On the other hand, a great number of known approaches exist for the synthesis of the structurally related PGA₂'s;⁶ therefore, a general method to swap from the A₂ to the J₂ family is highly desirable as a practical

CHART 1. Some Representative Examples of Cyclopentenone Prostaglandins



alternate means to achieve this important class of biologically active compounds.

In this note we report for the first time a versatile approach to transform an advanced A₂ synthetic intermediate into a suitable synthon for the J₂ synthesis. This A–J prostaglandin swap should allow one to capitalize on almost all the already developed approaches to prepare PGA₂'s for the synthesis of J₂ analogues. A common intermediate described in the PGA₂ synthesis was the allylic alcohol **4**;^{6b} therefore, an efficient allylic 1,3-transposition across the allylic alcohol was envisioned to furnish the advanced precursor **5** for J₂ prostaglandin synthesis (Scheme 1).

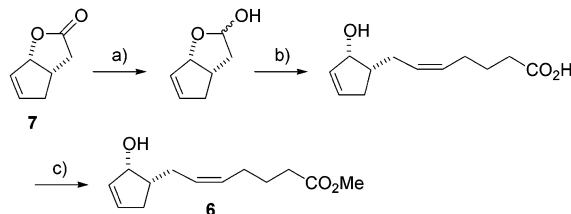
To achieve the best procedure to perform the A–J swap, we explored a few allylic rearrangement tactics on the model compound **6** (Scheme 2).⁷ The task proved to be not trivial.

In fact, a number of appealing 1,3-allylic transposition reactions, in principle amenable to accomplish the expected A–J swap, proved to be unfeasible for the allylic alcohol **6**. In the event, rearrangement of epoxy alcohol **9** according to the Li's procedure (path a–b) afforded the desired allyl alcohol **8** in an unsatisfactory 12% overall

(5) To date only a limited number of total syntheses have been reported in the literature: (a) Ali, S. M.; Chapleo, B. C.; Finch, M. A. W.; Roberts, S. M.; Wooley, G. T.; Cave, R. C.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2093–2097. (b) Bundy, G. L.; Morton, D. R.; Peterson, D. C.; Nishizawa, E. E.; Miller, W. L. *J. Med. Chem.* **1983**, *6*, 790–799. (c) Ali, M. S.; Finch, M. A. W.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Chem. Commun.* **1979**, 679–682.

(6) (a) Krafft, M. E.; Wright, C. *Tetrahedron Lett.* **1992**, *33*, 151–152 and references therein. (b) ApSimon, J. *The Synthesis of Prostaglandins*, Vol. 4, The Total Synthesis of Natural Product; Bindra, J. S., Ed.; Wiley-Interscience Publication: New York, 1981; pp 353–449.

(7) (a) Compound **6** was readily prepared in three synthetic steps from the known lactone **7**.^{7b}



a) DIBAL-H, DCM, -78°C, 90%; b) [Ph₃P(CH₂)₄COOH]Br, t-BuOK, THF, r.t., 86%; c) CH₂N₂, Et₂O, 0°C, 88%

(b) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298–5300.

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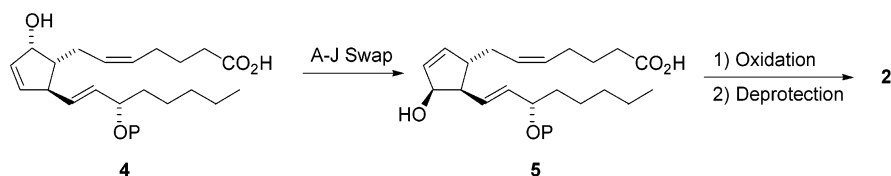
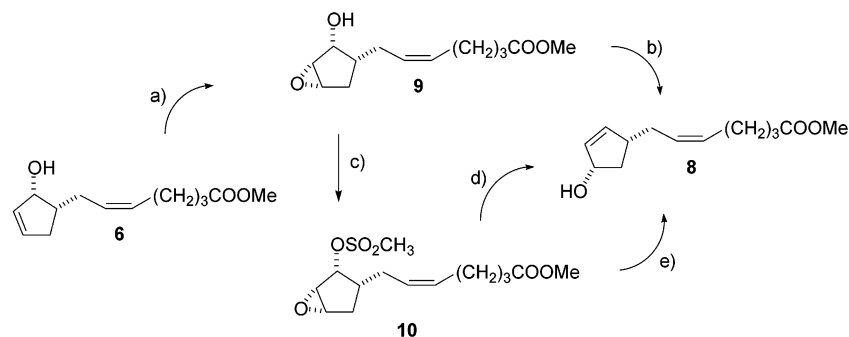
(1) Neghishi, M.; Katoh, H. *Prostaglandins Lipid Mediators* **2002**, *68–69*, 611–617 and references therein.

(2) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185–210 and references therein.

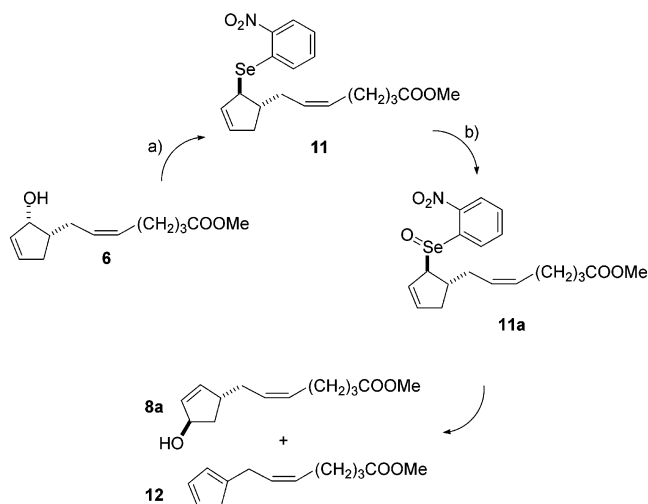
(3) Rossi, A.; Elia, G.; Santoro, M. G. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 746–750.

(4) (a) Forman, B. M.; Tontonoz, P.; Brun, R. P.; Spiegelman, B. M.; Evans, R. M. *Cell* **1995**, *83*, 803–812. (b) Kliewer, S. A.; Lenhard, J. M.; Willson, T. M.; Patel, I.; Lehmann, J. M. *Cell* **1995**, *83*, 813–819.

SCHEME 1

SCHEME 2^a

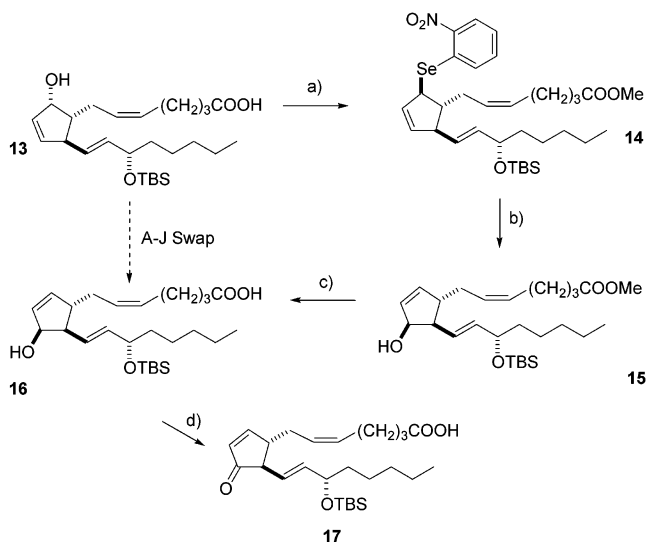
^a Reagents and conditions: (a) *t*-BuOOH, VO(acac)₂, DCM, 0 °C, 70%; (b) (i) I₂, Ph₃P, Py, Et₂O–MeCN (5:3), rt; (ii) H₂O, 40 °C, 17%; (c) CH₃SO₂Cl, Et₃N, –15 °C, 97%; (d) Te, NaBH₄, DMF, 40 °C, 68%; (e) NaI, Zn, DMF, 100 °C, 71%.

SCHEME 3^a

^a Reagents and conditions: (a) *o*-nitrophenyl selenocyanate, Bu₃P, THF, rt, 92%; (b) H₂O₂ 30%, Py, 7 °C, THF, 66%.

yield;⁸ the Dittmer's telluride-mediated transposition reaction (path a–c–d) of methansulfonate **10** afforded alcohol **8** in 46% overall yield,⁹ while the reductive epoxide ring opening of compound **10** (path a–c–e) performed only slightly better, furnishing cyclopentenol **8** in 48% overall yield from **6**.¹⁰

Considering the unsatisfactory results of the above approaches, we were forced to develop a more abbreviated A–J swap protocol that involves the [2,3] sigmatropic rearrangement of secondary allylic selenoxide **11a** (Scheme 3).¹¹

SCHEME 4^a

^a Reagents and conditions: (a) (i) CH₂N₂, Et₂O, 0 °C, quant.; (ii) *o*-nitrophenyl selenocyanate, Bu₃P, THF, rt, 78%; (b) H₂O₂ 30%, Py, 7 °C, THF, 55%; (c) Ba(OH)₂·8H₂O, MeOH, rt, 73%; (d) DMP, DCM, rt, 80%.

On exposure to *o*-nitrophenyl selenocyanate in the presence of tri-*n*-butylphosphine, alcohol **6** readily afforded the S_N2 selenide product **11** in 92% yield.¹² Subsequent oxidation of compound **11** with 30% H₂O₂ in the presence of pyridine in THF at 7 °C proceeded smoothly, giving the desired alcohol **8a** along with a small quantity (8% isolated yield) of diene **12**.

The transposed epimeric allyl alcohol **8a** was thus obtained in a gratifying 60% overall yield starting from cyclopentenol **6**.

It should be pointed out that the stereochemical outcome of this crucial transposition has no consequence in our synthetic plan since one of the last steps requires the oxidation of the transposed allylic alcohol to the corresponding α,β-unsaturated ketone.

(8) Liu, Z.; Lan, J.; Li, Y. *Tetrahedron: Asymmetry* **1998**, 9, 3755–3762.

(9) Discordia, R. P.; Murphy, C. K.; Dittmer, D. C. *Tetrahedron Lett.* **1990**, 31, 5603–5606.

(10) Nemoto, H.; Matsuhashi, N.; Satoh, A.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 495–498.

With an A–J swap protocol in hand we then turned our attention to the preparation of an advanced intermediate for the PGJ₂ synthesis (Scheme 4). To this aim the fully functionalized hydroxyacid **13** used in the Roberts synthesis of PGA₂ was prepared and subjected to the A–J swap.¹³

Thus, compound **13** was first converted to the corresponding methyl ester and then exposed to *o*-nitrophenyl selenocyanate and Bu₃P in THF.

The S_N2 selenide product **14** was obtained in a gratifying 78% isolated yield over two steps. Subsequent oxidation of **14** with 30% H₂O₂ in the presence of pyridine at 7 °C in THF promoted the [2,3] sigmatropic rearrangement of the intermediate allylic selenoxide to yield the epimeric alcohol **15** along with a small amount of elimination products arising from syn elimination of seleninic acid.

Hydrolysis of methyl ester **15** with Ba(OH)₂ afforded the pure hydroxy acid **16** in 40% yield over two steps.

(11) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154–7155. (b) Zoretic, P. A.; Chambers, R. J.; Marbury, G. D.; Riebiro, A. A. *J. Org. Chem.* **1985**, *50*, 2981. (c) For some application of [2,3] sigmatropic rearrangement of allylic selenoxide see: Back, T. G.; McPhee, D. J. *J. Org. Chem.* **1984**, *49*, 3842–3843. Koprowski, M.; Krawczyk, E.; Skowrońska, A.; McPartlin, M.; Choi, N.; Radojievic, S. *Tetrahedron* **2001**, *57*, 1105–1118.

(12) Grieco, P. A.; Gilman, M.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(13) Chapleo, B. C.; Finch, M. A. W.; Roberts, S. M.; Lee, T. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2084–2087.

Finally, Dess–Martin oxidation of alcohol **16** furnished ketone **17**, the penultimate intermediate of Roberts total synthesis of prostaglandin J₂.

In conclusion, a practical methodology for the J prostaglandins synthesis has been developed starting from the well-consolidated approaches established for the A prostaglandins chemistry. Application of the A–J swap has been used either for the formal synthesis of *rac*-PGJ₂ starting from the advanced intermediate **13** or for the first enantioselective synthesis of natural (8*S*,12*R*,15*S*) PGJ₂ **2**. Further application of the same A–J swap in the isoprostane field is currently actively under investigation in our laboratory and will be reported elsewhere.

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Supporting Information Available: Experimental procedures for the swap protocol, along with the synthesis and characterization for compounds **8**, **8a**, **9**, **10**, **11**, **14**, **16**, and **17**, and the preparation of ester **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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