JOC*Note*

First Enantioselective Total Synthesis of (8*S*,12*R*,15*S*)-Prostaglandin J_2

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Abstract: Enantioselective synthesis of natural PGJ_2 has been accomplished for the first time starting from the commercially available enantiopure aldehyde **7** in 10% overall yield. The key reaction was a novel prostaglandin class interconversion, i.e., an allylic 1,3-transposition across alcohol **9** derived from compound **14** in 73% overall yield. In principle, the unnatural enantiomer of PGJ_2 could be obtained starting from the commercially available enantiopure monobenzoate **7a** following our strategy.

Prostaglandin J_2 (PGJ_2) **1** was first reported in 1976 by Colton and Chinn in a study aimed at finding new postaglandin derivatives endowed with antispasmodic activity.[1] Some years later, Fukushima and Willis discovered that cyclopentenone PGJ_2 is also formed in vivo by dehydration within the cyclopentenone ring of the endogenous prostaglandin PGD_2 **2** (Chart 1).[2] The same reaction has been reproduced in vitro.

As a consequence of these intracellular events, i.e., the COXs (COX-1 and COX-2)-mediated arachidonic acid cascade, PGJ_2 was initially named 9-deoxy-Δ^9-PGD_2.[3] PGJ_2 is further metabolized to Δ^{12}-PGJ_2 **3** and then to 15-deoxy-$\Delta^{12,14}$-PGJ_2 **4** in a nonenzymatic fashion. Cyclopentenone prostaglandins of the J_2 series have their own unique spectrum of biological effects, including antitumor, antiinflammatory, and antiviral activities.

In addition, they are reported to inhibit cell cycle progression, to suppress viral replication, and to stimulate osteogenesis, apoptosis, and the expression of stress-related genes in various cell types including human breast cancer cells.[4]

Despite the burgeoning new biological activities associated with PGJ_2, surprisingly its enantioselective total synthesis is still waiting to be accomplished. Besides the total synthesis of (±)-PGJ_2 reported by Roberts and Newton,[5] the other published racemic approaches are

CHART 1. COXs Mediated Arachidonic Acid Cascade

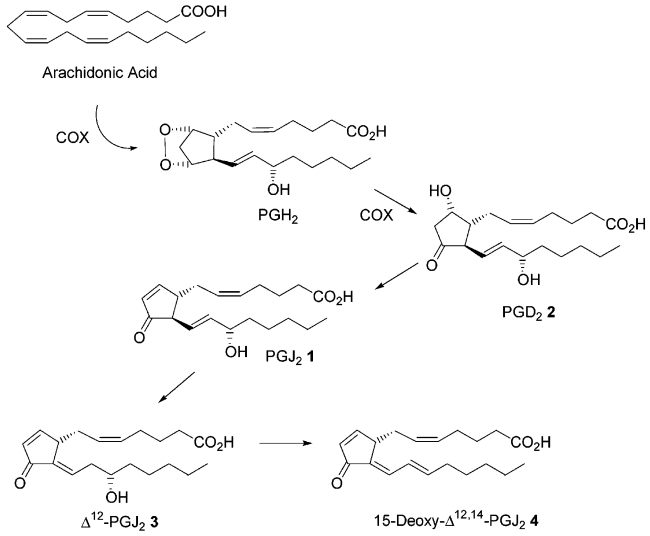
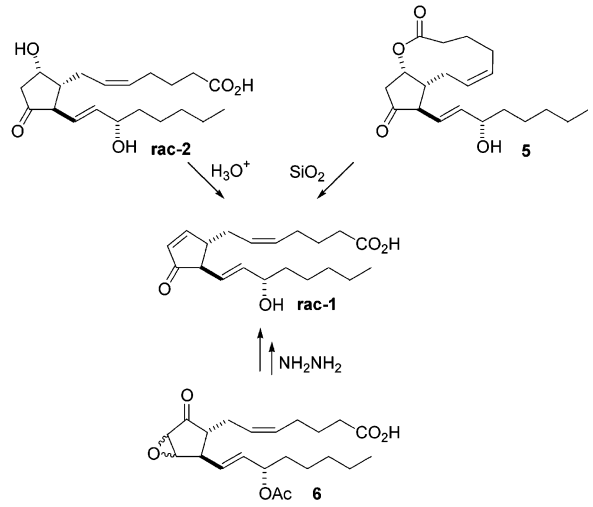


CHART 2



based on (i) acid-mediated dehydration of the corresponding PGD_2 **2**,[6] (ii) SiO_2-mediated rearrangement of prostaglandin-lactone **5**,[7] and (iii) hydrazine mediated rearrangement of epoxy-PGA_2 derivative **6**[1] (Chart 2).

To explore the role of enantioselectivity in the biological activities of PGJ_2, an asymmetric synthesis of both enantiomers of prostaglandin J_2 is therefore highly desirable. In this paper, we describe the first enantioselective route to natural (+)-(8*S*,12*R*,15*S*)-prostaglandin J_2 **1**, which could be applied for the preparation of the (−)-(8*R*,12*S*,15*R*) enantiomer.

Our synthetic strategy, illustrated in Scheme 1, takes advantage of two important synthetic bonuses: (i) the commercial availability of multigram amounts of either

(1) Colton, F. B.; Chinn, L. J. U.S. Patent 3 954 844, 1976.

(2) (a) Fukushima, M.; Kato, T.; Ota, K.; Narumiya, S. *Biochem. Biophys. Res. Commun.* **1982**, *109*, 626−633. (b) Mahmud, I.; Smith, D. L.; Whyte, M. A.; Nelson, J. T.; Cho, D. Tokes, Alvarez, L. G.; Willis, A. L. *Prostaglandins Leukotrienes Med.* **1984**, *16*, 131−146.

(3) Nosjean, O.; Boutin, J. A. *Cell. Signaling* **2002**, *14*, 573−583.

(4) (a) Kliewer, S. A.; Lenhart, J. M.; Willson T. M.; Patel, I.; Lehmann, J. M. *Cell* **1995**, *83*, 813−819. (b) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185−210 and references therein. (c) Negishi, M.; Katoh, H. *Prostaglandins Other Lipid Mediators* **2002**, *68*−*69*, 611−617.

(5) (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) Ali, M. S.; Finch, M. A. W.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Chem. Commun.* **1979**, 679−682.

(6) Morton, D. R., Jr. U.S. Patent 4 016 184, 1977.

(7) Bundy, G. L.; Morton, D. R.; Peterson, D. C.; Nishizawa, E. E.; Miller, W. L. *J. Med. Chem.* **1983**, *6*, 790−799. The racemic modification of PGJ_2 was obtained by these authors; see ref 3 in: Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1383−1386.

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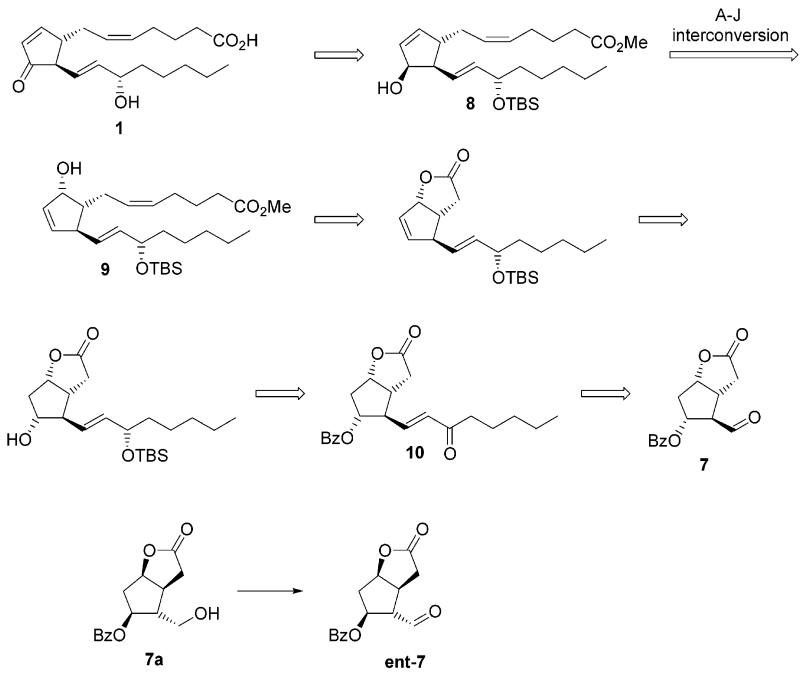
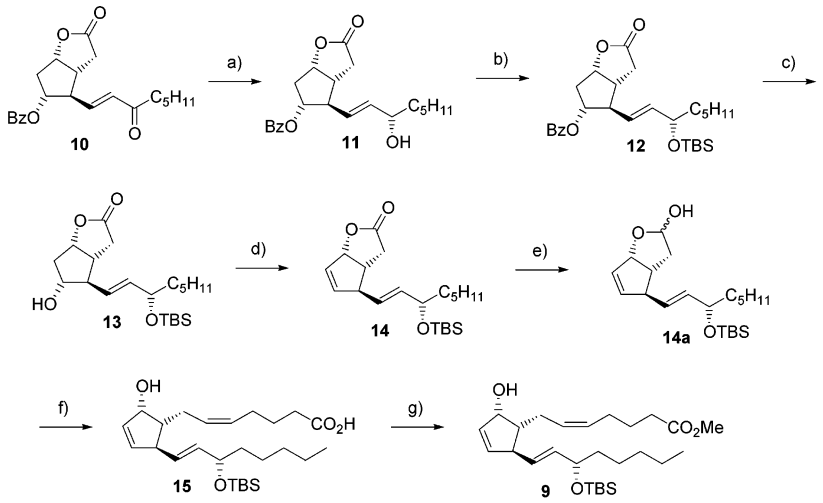
SCHEME 1. Retrosynthetic Sequence for Prostaglandin 1



SCHEME 2[a]



[a] Key: (a) (*S*)-BINAl, EtOH, THF, −100 °C, 1 h, 80%; (b) TBDMSCl, imidazole, DMAP, DCM, rt, 4.5 h, 95%; (c) K_2CO_3, MeOH, rt, 36 h, 98%; (d) DEAD, Ph_3P, THF, rt, 5.5 h, 76%; (e) DIBAL-H, DCM, −78 °C, 1 h, 96%; (f) $Ph_3P(CH_2)_4COOH$, *t*-BuOK, THF, rt, 20 min, then **14a** in THF, rt, 1 h, 84%; (g) CH_2N_2, Et_2O, rt, 90%.

synthons for **1** and for **ent-1** in enantiopure forms, aldehyde **7** and monobenzoate **7a**, respectively;[8] (ii) an efficient protocol for the A−J prostaglandins interconversion, namely for the conversion of allylic alcohol **9** to the rearranged cyclopentenol **8**.

According to our plan, the first part of our synthesis required the preparation of cyclopentenol **9,** which we envisioned to obtain in a few steps from the known enone **10**. The latter is readily prepared from enantiopure aldehyde **7** with a standard Wadsworth−Horner−Emmons reaction following the Bundy's original protocol.[9]

With enone **10** in hand, the synthesis of **9** proceeded uneventfully as outlined in Scheme 2. Chemo- and enantioselective reduction of the α,*β*-unsaturated carbonyl group was carried out following the Noyori procedure.[10]

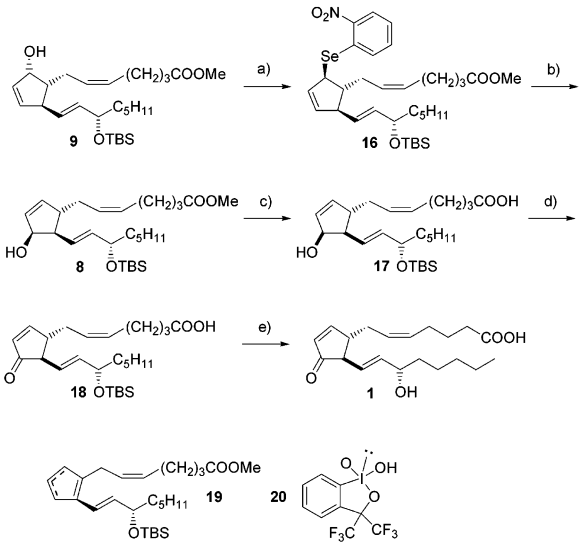
Accordingly, reduction of enone **10** at −100 °C with (*S*)-BINAl prepared in situ in THF, afforded the desired 15-*S* alcohol **11** in 80% isolated yield as a single stereoisomer (HPLC analysis). After protection of the C-15 hydroxyl group as *tert*-butyldimethylsilyl ether **12** (95% yield), the double bond inside the five-membered ring was installed by a Wierenga dehydration of cyclopentanol **13**. In the

(8) CaymannChemical, Cayman Chemical Co., 1180 East Ellsworth Road, Ann Arbor, MI 48108.

(9) Yankee, E. W.; Axen, U.; Bundy, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 5865−5876.

(10) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6716.

SCHEME 3[a]

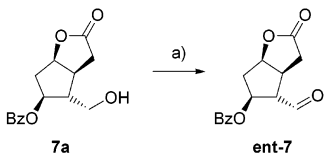


[a] Key: (a) *o*-nitrophenyl selenocyanate, Bu_3P, THF, rt, 80%; (b) H_2O_2 30%, Py, 0 °C, THF; (c) $Ba(OH)_2 \cdot 8H_2O$, MeOH, rt, 52% over two steps; (d) **20**, AcOH, DCM, 80%; (e) 48% aq HF, MeCN, −20 °C, 88%.

event, benzoate ester **12** was cleaved with a catalytic amount of K_2CO_3 in dry MeOH at rt for 36 h to afford the corresponding alcohol **13** (98% isolated yield) that upon exposure to DEAD and Ph_3P in THF readily produced the desired olefin **14** in a gratifying 76% isolated yield.[11]

This new route to lactone **14** ($[\alpha]^{20}_D = +203.5$, *c* 0.96, CH_2Cl_2; lit.[12] $[\alpha]^{21}_D = +159$, *c* 0.85, $CHCl_3$; lit.[12a] $[\alpha]^{22}_D = +161.5$, *c* 2.8, $CHCl_3$) represents a significant improvement with respect to existing methods and could be applied to deliver grams of this advanced intermediate for the asymmetric synthesis of PGA_2 in 46% overall yield from aldehyde **7**. The synthesis of key cyclopentenol **9** proceeded straightforwardly from lactone **14** in a few additional steps. Thus, standard olefination of the aldehyde function reductively released from lactone **14** (DIBAL-H, DCM, −78 °C, 1 h, 96%) with the nonstabilized Wittig reagent prepared from $Ph_3P(CH_2)_4COOH$ and *t*-BuOK in THF smoothly gave the corresponding *Z* olefin **15** in 84% yield.[13] Methyl ester **9** was then obtained in 90% isolated yield by exposure of carboxylic acid **15** to ethereal solution of CH_2N_2. The crucial interconversion of cyclopentenol **9** to the corresponding alcohol **8**, required for the completion of the PGJ_2 synthesis, was accomplished according to our recently introduced A−J swap protocol (Scheme 3). In the event, cyclopentenol **9** was converted to the corresponding selenide **16** (*o*-nitrophenyl selenocyanate, Bu_3P in THF, rt, 1.5 h, 80%) which was immediately oxidized with 30% H_2O_2 in the presence of pyridine in THF at 0 °C for 20 h. Concomitant [2,3] sigmatropic rearrangement of the intermediate allylic selenoxide afforded the desired alcohol **8**, contaminated by an unidentified, chromatographically inseparable product, along with a mixture of olefins **19** (15% isolated yield). Deprotection of methylester with $Ba(OH)_2$ in methanol, followed by a chromatographic separation, afforded pure hydroxy acid **17** in 52% yield over two steps from **16**. Mild oxidation of the sensitive cyclopentenol **17** to the stereochemically labile ketone **18** was achieved employing hydroxyiodinane oxide **20** in DCM and in the presence of 1.2 equiv of AcOH.[14] The target cyclopentenone **1** was finally obtained by aqueous HF mediated desilylation of silyl ether **18** in MeCN at −20 °C.[15] The ^1H NMR spectrum of **1**, $[\alpha]^{20}_D = +177$ (*c* 1, CH_2Cl_2), was identical to that recorded for natural PGJ_2 commercially available from Cayman[8]

SCHEME 4[a]



[a] Key: (a) DMP, CH_2Cl_2, rt, 92%.

Asymmetric synthesis of **ent-1** should be accomplished following the same reactions sequence starting from the **ent-7** easily prepared from Dess−Martin oxidation of monobenzoate **7a** (Scheme 4).

In conclusion, the first asymmetric synthesis of (8*S*,12*R*,15*S*)-PGJ_2 **1** has been accomplished in 10% overall yield starting from enantiopure aldehyde **7**, commercially available in multigram amounts. In addition, the key intermediate for the asymmetric synthesis of PGA_2, e.g., lactone **14**, has been stereoselectively prepared in a very efficient way (46% overall yield) from aldehyde **7**. Biological evaluation of both enantiomers of prostaglandin J_2 is under way and will be reported in due course.

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Supporting Information Available: Experimental procedures for synthesis and characterization for compounds **9**−**18**, **ent-7,** and the target compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Dow, R. L.; Kelly, R. C.; Schletter, I.; Wierenga, W. *Synth. Commun.* **1981**, *11*, 43−53.
(12) (a) Kobayashi, Y.; Muruges, M. M.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110−7123. (b) Newton, R. F.; Reynolds, D. P.; Davies, J.; Kay, P. B.; Roberts, S. M.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 683−685.
(13) Chapleo, C. B.; Finch, M. A. W.; Lee, T. V.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2084−2087.
(14) (a) VanderRoest, J. M.; Grieco, P. A. *J. Org. Chem.* **1996**, *61*, 5316−5325. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(15) Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Tetrahedron Lett.* **1979**, *41*, 3981−3982.