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Total synthesis of Δ^{12}-PGJ_2, 15-deoxy-$\Delta^{12,14}$-PGJ_2, and related compounds

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Abstract—A key cyclopentenone possessing the α-chain was synthesized from TBS ether of 4-cyclopentene-1,3-diol monoacetate, and submitted to aldol reaction at the α′-position with the ω-chain aldehydes followed by dehydration to produce the title compounds. In a similar manner, 5-dehydro compounds (acetylene analogues) were synthesized successfully. In addition, palladium-catalyzed reaction of 4-cyclopentene-1,3-diol monoacetate with methyl malonate, the first step of the synthesis, was improved to afford the product in high yield by using *t*-BuOK or LDA in place of NaH.

Δ^{12}-Prostaglandin J_2 (Δ^{12}-PGJ_2) and 15-deoxy-$\Delta^{12,14}$-PGJ_2 are products derived from PGJ_2 in vivo,[1] and were reported in the 1980s to possess important biological activities.[2] In the 1990s these compounds were shown to be ligands for peroxisome proliferator-activated receptors (PPARs), the nuclear receptors, which regulate gene transcription directly.[3,4] In such studies, the compounds have been supplied by companies.[5,6] However, total synthesis of the compounds was not published until quite recently,[7] though a synthetic effort apparently will accelerate biological study. Recently, synthesis of Δ^7-PGA_1 methyl ester was achieved in our laboratory.[8] The assured aldol reaction at the α′ position of enones and the structural similarity between Δ^7-PGA_1 methyl ester and the title compounds encouraged us to develop synthetic strategy through aldol reaction of cyclopentenone **6** with aldehyde **7** (for Δ^{12}-PGJ_2, Scheme 1) or 2-octenal (15-deoxy-$\Delta^{12,14}$-PGJ_2) to assemble the core structures. Herein, we present a synthesis of Δ^{12}-PGJ_2 (**2**), 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**3**), and 5-dehydro analogues (Fig. 1).

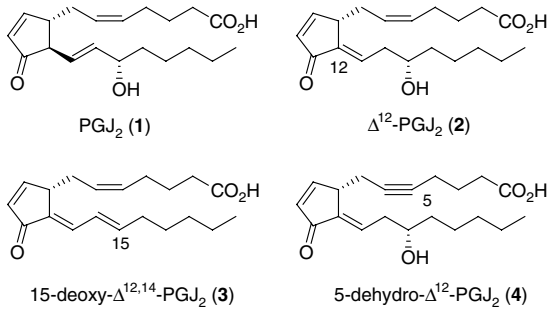
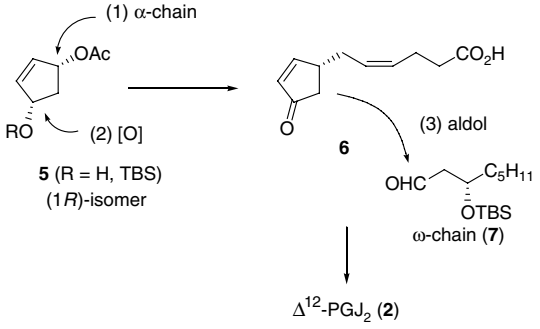


Figure 1. PGJ_2 and related PGs.

In order to realize the approach outlined above, we initially examined synthesis of the key intermediate **10** depicted in Scheme 2 by a sequence through alcohol **8a**. Palladium-catalyzed reaction of monoacetate **5a** with the anion derived from methyl malonate (2–2.5 equiv) and NaH (2 equiv) in THF at 40–50 °C, according to Deardorff,[9] produced **8a** in varying yields of ca. 50–70%



Scheme 1. Strategy for synthesis of Δ^{12}-PGJ_2.

Keywords: Δ^{12}-PGJ_2; 15-Deoxy-$\Delta^{12,14}$-PGJ_2; 4-Cyclopentene-1,3-diol monoacetate; Palladium catalyst; Aldol reaction; Cyclopentenone.
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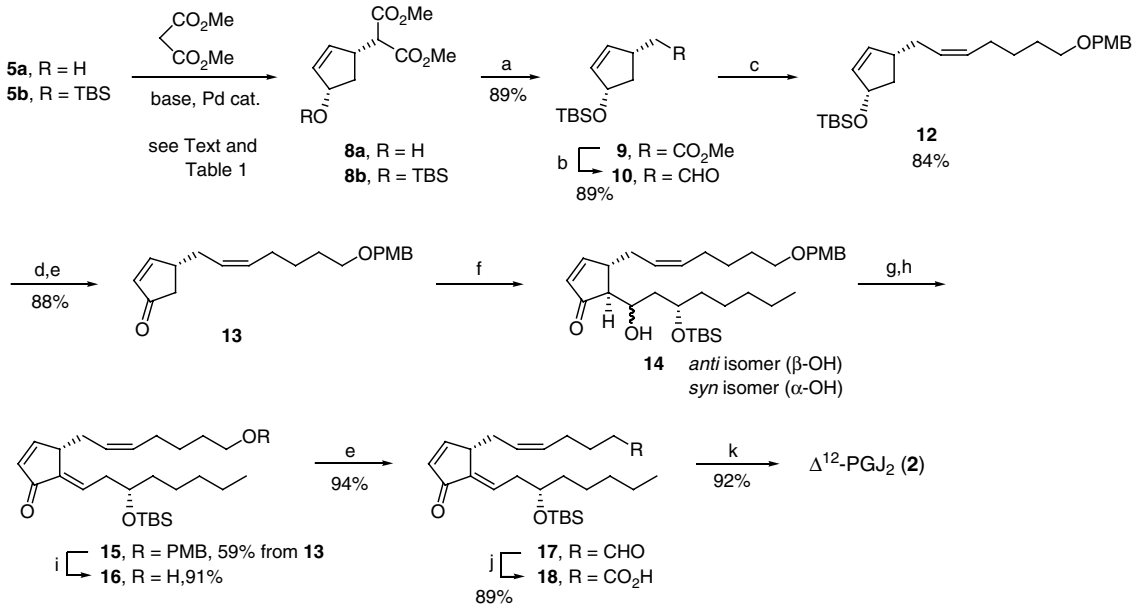


Scheme 2. Synthesis of Δ^{12}-PGJ$_2$. Reagents and conditions: (a) KI, DMI/H_2O (10:1), 130 °C; (b) DIBAL, CH_2Cl_2, −78 °C; (c) $[Ph_3P(CH_2)_5\ OPMB]^+Br^-$ (**11**) (2.0 equiv), $NaN(TMS)_2$ (2.0 equiv), −70 °C to rt; (d) TBAF; (e) PCC; (f) LDA (2.0 equiv), −78 °C, THF then **7** (1.2 equiv), −78 °C; (g) MsCl, Et_3N, 0 °C; (h) Al_2O_3, CH_2Cl_2; (i) DDQ, CH_2Cl_2/H_2O (19:1); (j) $NaClO_2$ (1.5 equiv), $MeCH=C(Me)_2$ (10 equiv), *t*-BuOH, phosphate buffer; (k) HF/MeCN (1:19).

Table 1. Palladium-catalyzed reaction with methyl malonate[a]

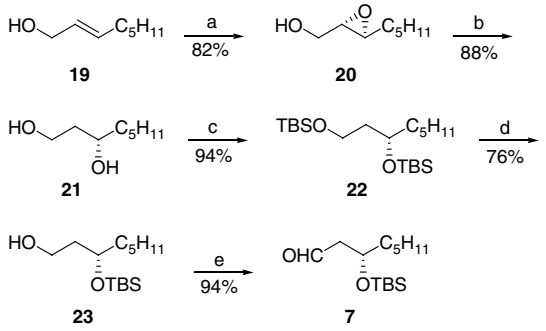
Entry	Substrate	Base	Time (h)	Temperature (°C)	Yield (%)
1	**5a**	NaH	2	rt	69[b,c]
2	**5a**	MeONa	2	rt	71[b]
3	**5a**	LDA	1.5	rt	83[b]
4	**5a**	*t*-BuOK	2	rt	90
5	**5b**	NaH	4	50[d]	66
6	**5b**	MeONa	3	50[d]	87
7	**5b**	LDA	3	rt	91
8	**5b**	*t*-BuOK	3	50[d]	93

[a] Reactions were carried out with methyl malonate (2.2 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol%) in THF.
[b] An unidentified by-product was also produced.
[c] A maximum yield among several repeated reactions is given. See the text for more information.
[d] No reaction at room temperature for 1 h was monitored by TLC.

after separation of the remaining malonate by using a somewhat long silica gel column due to close mobilities on TLC. Reactions attempted in polar solvents, at lower temperatures, and/or with additional ligand (PPh_3) for the palladium catalyst ($Pd(PPh_3)_4$) did not improve the yield and reproducibility. In addition, after decarboxylation of **8a**, tedious chromatography was again necessitated for purification of the crude product containing the polar solvent used (such as DMF, 1,3-dimethyl-2-imidazolidinone (DMI), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), etc.). For these reasons, we re-examined the reactions leading to **10**.

Among the bases listed in Table 1 (MeONa, LDA, *t*-BuOK), LDA and *t*-BuOK were found to be the choice. The reactions with these bases took place at room temperature to afford product **8a** in good yields after chromatography (entries 3 and 4). We then applied these bases to TBS ether **5b**, derived from **5a** by silylation in 94% yield, since separation of product **8b** and methyl malonate is easier work than that of alcohol **8a** and the malonate. Reaction with LDA proceeded at room temperature, while *t*-BuOK required a higher temperature of 50 °C, in both cases producing **8b** in high yields (entries 7 and 8). With regard to the product yields, reaction temperatures, and preparation/handling of the bases, we do recommend both bases. Decarboxylation of **8b** with KI in wet DMI proceeded well, and isolation/purification of TBS ether **9** from DMI was accomplished quite easily because of the lower polarity of **9**. Finally, reduction of **9** with DIBAL at −78 °C furnished aldehyde **10** in 89% yield.

Wittig reaction of aldehyde **10** with the anion derived from $[Ph_3P(CH_2)_5OPMB]^+Br^-$ (**11**) and $NaN(TMS)_2$ at room temperature, according to the literature procedure,[10] proceeded with high stereoselectivity to afford *cis* olefin **12** in 84% yield. Setting up the reaction initially at low temperature (ca. −70 °C) was important since use of



Scheme 3. Preparation of aldehyde **7**. Reagents and conditions: (a) *t*-BuOOH (1.4 equiv), L-(+)-DIPT (0.3 equiv), Ti(*i*-PrO)$_4$ (0.25 equiv), MS 4A; (b) Red-Al (2.0 equiv), THF; (c) TBSCl; (d) PPTS (1.2 equiv), EtOH/CH_2Cl_2 (1:1); (e) PCC.

0 °C at the beginning resulted in production of a minor compound detected by ^{13}C NMR spectroscopy (ca. 5%), which is probably responsible for the *trans* olefin isomer. Next, the two-step conversion of **12** into enone **13** proceeded smoothly. Enone **13** is a compound, which is corresponding to the key intermediate **6** depicted in Scheme 1.

Although the enantiomer is a known compound,[11] aldehyde **7** (Scheme 1), the aldol partner of enone **13**, was synthesized from commercially available alcohol **19** through epoxy alcohol **20**[12] ($[\alpha]_D^{24}$ −43° (*c* 0.45, $CHCl_3$); lit.[12] $[\alpha]_D^{25}$ −42.7° (*c* 4.7, $CHCl_3$)) in five steps in 48% overall yield (Scheme 3): $[\alpha]_D^{27}$ +6.7° (*c* 0.21, $CHCl_3$) for **7** synthesized; lit.[11] $[\alpha]_D^{24}$ −5.0° (*c* 1.0, $CHCl_3$) for the enantiomer. Synthetic advantages of this method are as follows. Epoxide ring opening proceeded with 22:1 regioselection by ^{1}H NMR spectroscopy to afford **21** in good yield. Regioselective desilylation of the bis-silyl ether **22** to mono alcohol **23** was accomplished in 76% yield with PPTS (1.2 equiv), which allowed us to bypass the rather conventional protection/deprotection steps.[13]

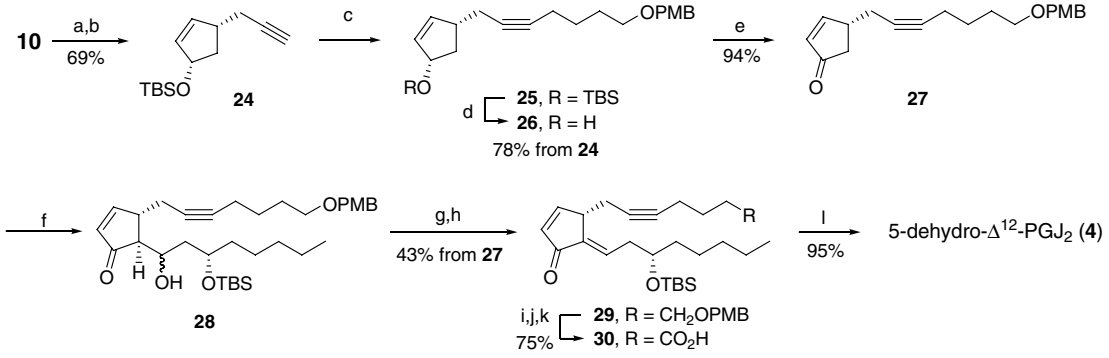
Aldol reaction of enone **13** with aldehyde **7** afforded a mixture of *anti* and *syn* isomers in a 3:1 ratio by ^{1}H NMR spectroscopy.[14] Without separation, the mixture was converted to mesylates, which were exposed to Al_2O_3 to afford dienone **15** in 59% yield from enone **13**. The stereochemistry of the newly formed olefin was assigned as depicted (*trans*) by the literature analogy[8,15] (H-C(13): δ 6.59 ppm, t, $J = 7.5$ Hz), while the corresponding *cis* olefin (structure not shown) was not detected by ^{1}H NMR spectroscopy.

The remaining transformation to Δ^{12}-PGJ$_2$ was functional group manipulation, which was accomplished successfully. Briefly, the PMB protective group of **15** was removed with DDQ in wet CH_2Cl_2 to afford alcohol **16**, which was converted to acid **18** through aldehyde **17** in 81% yield from **15**. Finally, deprotection of the TBS group with HF in MeCN afforded Δ^{12}-PGJ$_2$ in 92% yield. Direct oxidation of **16** with PDC in DMF at room temperature overnight produced a mixture of products. The ^{1}H NMR spectrum of synthetic **2** was identical with that reported (δ 5–8 ppm)[1a] and also provided by Ono Pharmaceutical Co., Ltd.

In a similar manner, aldol reaction of **13** with (*E*)-2-octenal followed by the same transformation as described above produced 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (**3**) efficiently. The structure of **3** thus synthesized was confirmed by comparison of the ^{1}H NMR (δ 5–8 ppm)[1a] and ^{13}C NMR (all peaks)[7] spectra with those reported.[16]

Since structural analogues, in general, have been important tools in pursuing biological investigation with various purposes, synthesis of 5-dehydro analogue of Δ^{12}-PGJ$_2$ was also investigated. As shown in Scheme 4, acetylene **24** was synthesized from aldehyde **10** by the Corey–Fuchs method,[17] and was submitted to alkylation with Br(CH$_2$)$_4$ OPMB to afford **25**, which upon desilylation with TBAF produced alcohol **26** in 78% yield. Oxidation produced the key enone **27** in good yield. The remaining transformation of enone **27** to 5-dehydro-Δ^{12}-PGJ$_2$ (**4**) was carried out through the same transformation as that shown in Scheme 2 for Δ^{12}-PGJ$_2$ (**2**).

In a similar way, 5-dehydro analogue of **3** (structure not shown) was also accomplished.



Scheme 4. Synthesis of acetylene analogue of Δ^{12}-PGJ$_2$. Reagents and conditions: (a) PPh_3 (4.0 equiv), CBr_4 (2.0 equiv), 0 °C, 30 min; (b) *n*-BuLi (2.5 equiv), −78 °C, 1 h; (c) *n*-BuLi (1.2 equiv), PMBO(CH$_2$)$_4$Br (1.2 equiv), THF/DMPU (4:1), −78 °C to rt; (d) TBAF; (e) PCC; (f) LDA (2.0 equiv) then **7** (1.2 equiv), −78 °C; (g) MsCl, Et_3N, 0 °C, 1 h; (h) Al_2O_3; (i) DDQ; (j) PCC; (k) $NaClO_2$ (1.5 equiv), MeCH=C(Me)$_2$, *t*-BuOH, phosphate buffer (pH 3.6); (l) HF/MeCN (1:19).

In summary, we have succeeded in synthesis of Δ^{12}-PGJ_2 (**2**), 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**3**), and acetylene analogues based on an aldol strategy starting with the TBS ether of monoacetate **5a**. Since preparation of **5a** has been established, high efficiency and flexibility of the present method will allow synthesis of analogues other than that mentioned in the text, thus spurring biological investigation. In addition, we established conditions for Pd-catalyzed reaction of **5** (R = H, TBS) with malonate anion, which would encourage use of products **8** (R = H, TBS) as key compounds in various fields.

Acknowledgements

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13. In contrast to the previous synthesis of the enantiomer,[11] the present method seems convenient with regard to the total number of steps including preparation of the aldol partner and the catalyst.
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16. The ^{1}H NMR spectrum of **3** at 500 MHz is presented below since the spectrum measured at 300 MHz was insufficient for determination of the olefin geometry at C(14)–(15): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, $J = 7$ Hz, 3H), 1.22–1.36 (m, 4H), 1.39–1.49 (m, 2H), 1.62–1.72 (m, 2H), 2.04 (q, $J = 7$ Hz, 2H), 2.18–2.37 (m, 5H), 2.56–2.62 (m, 1H), 3.56–3.61 (m, 1H), 5.33–5.40 (m, 1H), 5.42–5.49 (m, 1H), 6.23 (dt, $J = 15$, 7 Hz, 1H), 6.31 (ddt, $J = 15$, 11, 1 Hz, 1H), 6.36 (dd, $J = 6$, 2 Hz, 1H), 6.95 (d, $J = 11$ Hz, 1H), 7.47 (ddd, $J = 6$, 2.5, 1 Hz, 1H). Note that the reference for the ^{1}H NMR spectrum of **3** is not indicated in Ref. 7, in which the authors state accordance of the ^{1}H NMR spectrum of **3** with that reported.
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