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Concise and Enantioselective Total Synthesis of 15-Deoxy-$\Delta^{12,14}$-Prostaglandin J_2

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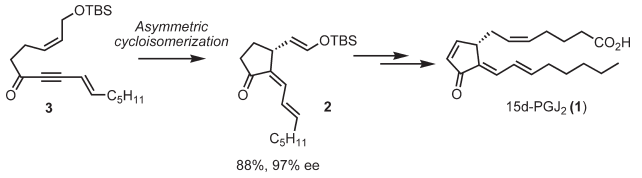
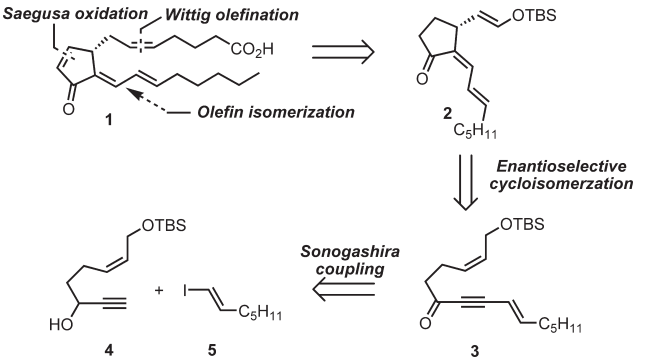


The concise and enantioselective synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ$_2$) has been accomplished in 11 steps from a known alcohol. The key step of the synthesis involves an asymmetric Rh-catalyzed cycloisomerization of ene-ynone, followed by an olefin isomerization.

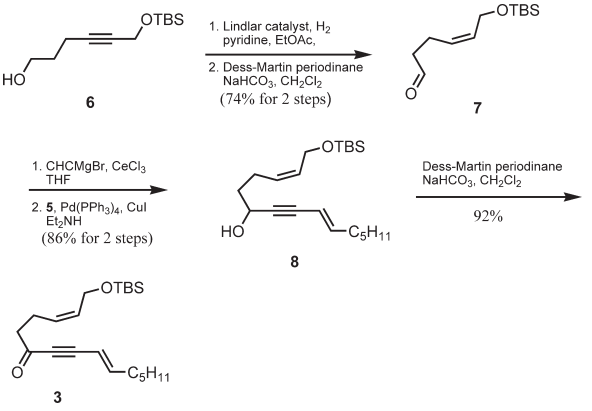
15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ$_2$), one of the most representative cyclopentenone prostaglandins, is known as an endogenous ligand of peroxisome proliferator-activated receptor γ (PPAR γ).[1] Recently it has received enormous attention due to its various biological functions such as anti-inflammatory, cytoprotective, proapoptotic, and anti-proliferative properties, which depend on cell types and concentrations.[2,3] The Keap-1/Nrf 2 complex as a regulator of homeostatic redox system has been a central focus of research in the past decade due to its potentiality as a chemopreventive target.[3] Thus, 15d-PGJ$_2$ is targeted as a probe for chemopreventive therapeutics[3] because 15d-PGJ$_2$ can serve as a potent ligand for the Keap-1 complex. In this context, optically active 15d-PGJ$_2$ has attracted increased attention in the fields of biological and medicinal chemistry. However, a versatile enantioselective synthesis of 15d-PGJ$_2$ that generates the stereogenic centers has not been previously described in the literature, although a few syntheses of this ligand from the pre-existing chiral unit have been reported.[4] Herein, we report the enantioselective total synthesis of 15d-PGJ$_2$ by employing an asymmetric Rh-catalyzed cycloisomerization of the ene-ynone precursor as the key step.

SCHEME 1. Retrosynthesis of 15d-PGJ$_2$ (1)



The retrosynthetic analysis of 15d-PGJ$_2$ is shown in Scheme 1. We pursued an enantioselective cycloisomerization[5] as a key reaction for ready access to both the crucial stereocenter and the core cyclopentanone system **2**, which can be effectively transformed into 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2. Intermediate **3** can also be conveniently prepared from known alcohol[6] **6** via sequential manipulations (Scheme 1).

SCHEME 2. Synthesis of the Precursor for Cycloisomerization



Our synthesis commenced with the partial hydrogenation of disubstituted alkyne **6**. The resulting allyl ether was converted into aldehyde **7** by Dess−Martin oxidation.[7] The addition of ethynyl magnesium bromide to aldehyde **7** in the presence of $CeCl_3$ provided propargyl alcohol,[8] which could be readily transformed into the enyne alcohol **8** by Sonogashira coupling with vinyl iodide **5**.[9] The Dess−Martin oxidation of alcohol **8** afforded ketone **3**, which is an appropriate precursor for the pivotal cycloisomerization (Scheme 2).

(1) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185–210.
(2) (a) Na, H. K.; Surh, Y. J. *Biochem. Pharmacol.* **2003**, *66*, 1381–1391. (b) Na, H. K.; Surh, Y. J. *Mol. Carcinog.* **2006**, *45*, 368–380.
(3) (a) Kim, E. H.; Surh, Y. J. *Biochem. Pharmacol.* **2006**, *72*, 1516–1528. (b) Dinkova-Kostova, A. T.; Holtclaw, W. D.; Kensler., T. M. *Chem. Res. Toxicol.* **2005**, *18*, 1779–1791.
(4) (a) Bickley, J. F.; Jadhav, V.; Roberts, S. M.; Santoro, G.; Steiner, A.; Sutton, P. W. *Synlett* **2003**, *8*, 1170–1174. (b) Acharya, H. P.; Kobayashi, Y. *Tetrahedron Lett.* **2004**, *45*, 1199–1202. (c) Acharya, H. P.; Kobayashi, Y. *Tetrahedron* **2006**, *62*, 3329–3343. (d) Brummond, K. M.; Sill, P. C.; Chen, H. *Org. Lett.* **2004**, *6*, 149–152.

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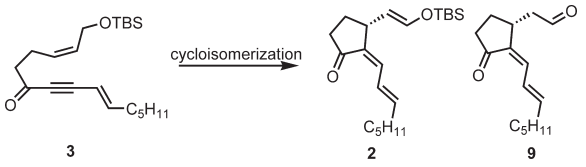
TABLE 1. Cycloisomerization of 3



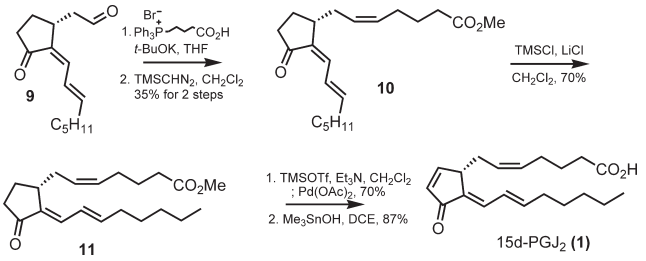
	condition	yield (%/% ee)
1	$[Rh(COD)Cl]_2$ 5 mol %, (*R*)-BINAP 12 mol %, $AgSbF_6$ 20 mol %, DCE	**2** (20), **9** (−)
2	$[Rh(COD)Cl]_2$ 10 mol %, (*R*)-BINAP 24 mol %, $AgSbF_6$ 40 mol %, DCE	**2** (40), **9** (10)
3	$[Rh(COD)Cl]_2$ 10 mol %, (*R*)-BINAP 24 mol %, $AgBF_4$ 40 mol %, DCE, 10 min	**2** (88/97[a]), **9** (−)
4	$[Rh(COD)Cl]_2$ 10 mol %, (*R*)-BINAP 24 mol %, $AgBF_4$ 100 mol %, DCE, 3 h	**2** (10/97[a]), **9** (61/97)

[a]Enantiomeric excess (ee) of **2** was confirmed by HPLC analysis of the corresponding aldehyde obtained by TBS deprotection.

Next, we addressed the formidable task of enantioselective cycloisomerization. An initial attempt employing the relevant conditions[10,11] resulted in the production of the desired TBS enol ether **2** in only 20% yield. Additional trial reactions with an increased amount of the catalyst did not provide substantial increase of the product. However, after intensive examination of the reaction conditions,[12,13] we finally observed that the cyclization of allyl ether **3** in dichloroethane under catalytic conditions using $[Rh(COD)Cl]_2$ and $AgBF_4$ in the presence of (*R*)-BINAP provided the desired TBS-enol ether **2** exclusively in good yield and stereoselectivity (88% yield, 97% ee on HPLC). Interestingly, a stoichiometric amount of $AgBF_4$ with $[Rh(COD)Cl]_2$ and (*R*)-BINAP at ambient temperature provided the exclusive formation of the desired aldehyde **9**, which is accessible via an additional deprotection of **2**, in 61% yield with 97% ee (Table 1).

With the key aldehyde **9** in hand, Wittig olefination introduced the acid side chain[4] and subsequent esterification with $TMSCHN_2$ afforded methyl ester **10**. The correct (*E*,*E*)-stereochemistry of diene **11** could be obtained from **10** in 70% yield by an olefin isomerization. The *Z*-exoenone isomer was effectively converted into the desired *E*-isomer by treatment with TMSCl and LiCl. The introduction of the ring-olefin to the cyclopentanone skeleton of **11** was achieved by the reaction of **11** with Et_3N and TMSOTf in CH_2Cl_2, followed by Saegusa[14] oxidation of the resulting TMS enol ether (Scheme 3). Having established a viable route to the requisite chiral methyl ester of **1**, the enantio selective synthesis of 15d-PGJ_2 was completed by ester hydrolysis using Me_3SnOH.[15] The spectral data (^1H NMR, ^{13}C NMR, HRMS, and specific rotation) of the synthetic 15d-PGJ_2 were in excellent agreement with the published data.[4]

SCHEME 3. Completion of 15d-PGJ_2 Synthesis



In conclusion, the concise and versatile enantioselective synthesis of 15d-PGJ_2 has been achieved via 11 reaction steps from a known alcohol. The key step includes an asymmetric Rh-catalyzed cycloisomerization of the ene-ynone precursor, followed by an olefin isomerization. Studies on the diverse biological functions and cellular signaling pathways of 15d-PGJ_2 based on the developed synthetic route are in progress.

Experimental Section

2-{(1*R*)-2-[(*Z*,2*E*)-2-Octenylidene]-3-oxocyclopentyl}acetaldehyde (9). To a solution of $[Rh(COD)Cl]_2$ (11 mg, 0.02 mmol) and (*R*)-BINAP (32 mg, 0.05 mmol) in dichloroethane (1 mL) was added ketone **3** (75 mg, 0.21 mmol) in dichloroethane (1 mL). The reaction mixture was stirred for 1 min. $AgBF_4$ (42 mg, 0.21 mmol) was added to the reaction mixture, which was then stirred until complete consumption of the starting material on TLC at ambient temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc:hexane = 1:5) afforded 31 mg (61%) of aldehyde **9** as a major product and 5 mg (10%) of enol ether **2** as a minor product. **2**: $[\alpha]^{20}_D$ −37.4 (*c* 0.22, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (dd, 1H, J = 15.6, 11.3 Hz), 6.34 (d, 1H, J = 11.9 Hz), 6.24 (dd, 1H, J = 11.5, 2.3 Hz), 6.00

(5) For comprehensive reviews, see: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067–2096. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834. (c) Fairlamb, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048–1052. (d) Michelet, V.; Toullec, P. Y.; Genet, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315.

(6) Balnaves, A. S.; McGowan, G.; Shapland, P. D. P.; Thomas, E. J. *Tetrahedron Lett.* **2003**, *44*, 2713–2716.

(7) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. (c) Williams, D. R.; Shamin, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. *Org. Lett.* **2003**, *5*, 3361–3364.

(8) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Pharm. Bull.* **1986**, *34*, 1531–1539.

(9) Takahashi, S.; Kuyoyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627–630.

(10) (a) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104–4106. (b) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526–4529. (c) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198–8199.

(11) (a) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11472–11473. (b) Liu, F.; Liu, Q.; He, M.; Zhang, X.; Lei, A. *Org. Biomol. Chem.* **2007**, *5*, 3531–3534.

(12) For comprehensive reviews of weakly coordinating counterions, see: (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927–942. (b) Reed, C. A. *Acc. Chem. Res.* **1998**, *31*, 133–139.

(13) For recent studies on cyclization employing another Rh(I) catalyst, see: (a) Rhee, J. U.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 10674–10675. (b) Jang, H. Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Broadbelt, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 6174–6175. (c) Jang, H. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 7875–7880.

(14) Ito, Y.; Hirao, Y.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

(15) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378–1382.

(dt, 1H, J = 15.3, 7.1 Hz), 4.87 (dd, 1H, J = 12.0, 9.0 Hz), 3.20 (m, 1H), 2.40−2.09 (m, 4H), 1.43−1.36 (m, 2H), 1.33−1.20 (m, 6H), 0.90 (s, 9H), 0.90−0.86 (m, 3H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.4, 145.6, 142.2, 137.7, 136.0, 126.4, 113.5, 42.1, 38.9, 33.0, 31.4, 29.0, 28.7, 25.7, 22.5, 18.4, 14.0, −5.2; LR-MS (FAB) m/z 349 ($M + H^+$); HR-MS (FAB) calcd for $C_{21}H_{37}O_2Si$ ($M + H^+$) 349.2563, found 349.2558. **9**: $[\alpha]^{20}_D$ +5.7 (c 0.17, MeOH); FT-IR (thin film, neat) ν_{max} 2927, 2857, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.85 (t, 1H, J = 1.4 Hz), 7.52 (dd, 1H, J = 15.2, 11.2 Hz), 6.23 (dd, 1H, J = 11.2, 2.0 Hz), 6.04 (dt, 1H, J = 14.9, 7.1 Hz), 3.30 (m, 1H), 2.77 (ddd, 1H, J = 17.4, 5.5, 0.9 Hz), 2.58 (ddd, 1H, J = 17.4, 8.1, 1.7 Hz), 2.39−2.14 (m, 4H), 1.60−1.21 (m, 8H), 0.90−0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.7, 200.9, 146.5, 137.0, 134.5, 126.2, 48.9, 38.4, 36.4, 33.0, 31.4, 28.6, 26.9, 22.4, 14.0; LR-MS (FAB) m/z 235 ($M + H^+$); HR-MS (FAB) calcd for $C_{15}H_{23}O_2$ ($M + H^+$) 235.1698, found 235.1688.

Methyl (*Z*)-7-{(1*R*)-2-[(*E*,2*E*)-2-Octenylidene]-3-oxocyclopentyl}-5-heptenoate (11). To a solution of exo (*Z*)-enone **10** (17 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added LiCl (15 mg, 0.36 mmol), followed by an addition of TMSCl (4 μL, 0.02 mmol) at 0 °C. The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was quenched with saturated aqueous Na_2HCO_3 and diluted with CH_2Cl_2. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc:hexane = 1:10) afforded 12 mg (70%) of **11**: $[\alpha]^{20}_D$ +106.3 (c 0.15, MeOH); FT-IR (thin film, neat) ν_{max} 1739, 1630, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91 (m, 1H), 6.21−6.19 (m, 2H), 5.45−5.42 (m, 2H), 3.64 (s, 3H), 3.08 (m, 1H), 2.44−1.72 (m, 10H), 1.47−1.20 (m, 10H), 0.90−0.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 173.9, 146.9, 138.5, 132.8, 130.8, 128.0, 126.4, 51.5, 39.0, 36.2, 33.4, 33.4, 32.4, 31.4, 28.4, 26.7, 24.8, 24.6, 22.5, 14.0; LR-MS (FAB) m/z 333 ($M + H^+$); HR-MS (FAB) calcd for $C_{21}H_{33}O_3$ ($M + H^+$) 333.2430, found 333.2441.

15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (1). To a solution of cyclopentanone **11** (33 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (20 μL, 0.14 mmol), followed by addition of TMSOTf (22 μL, 0.12 mmol) at 0 °C. The reaction mixture was stirred until complete consumption of the starting material on TLC at 0 °C. Then $Pd(OAc)_2$ (112 mg, 0.50 mmol) and benzoquinone (54 mg, 0.50 mmol) in acetonitrile were added to a solution of TMS enol ether at 0 °C. The reaction mixture was stirred for 4 h, quenched with H_2O, and then diluted with CH_2Cl_2. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc:hexane = 1:5) afforded 23 mg (70%) of methyl ester: $[\alpha]^{20}_D$ +121.2 (c 0.42, MeOH); FT-IR (thin film, neat) ν_{max} 1739, 1695, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (dd, 1H, J = 6.0, 2.6 Hz), 6.93 (d, 1H, J = 10.8 Hz), 6.34−6.16 (m, 3H), 5.48−5.30 (m, 2H), 3.63 (s, 3H), 3.54 (m, 1H), 2.57 (m, 1H), 2.36−2.17 (m, 5H), 2.04−1.97 (m, 2H), 1.69−1.57 (m, 2H), 1.48−1.22 (m, 6H), 0.87 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.3, 173.9, 160.6, 146.9, 135.2, 134.9, 131.6, 131.4, 125.9, 125.7, 51.5, 43.5, 33.4, 33.4, 31.4, 30.8, 28.4, 26.6, 24.7, 22.4, 14.0; LR-MS (FAB) m/z 331 ($M + H^+$); HR-MS (FAB) calcd for $C_{21}H_{31}O_3$ ($M + H^+$) 331.2273, found 331.2274. To a solution of the above methyl ester (14 mg, 0.04 mmol) in dichloroethane (1 mL) was added Me_3SnOH (72 mg, 0.40 mmol) at ambient temperature. The reaction mixture was refluxed overnight, quenched, and acidified with 2N HCl. The mixture was diluted with EtOAc and the organic phase was washed with 2N HCl solution several times and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc:hexane:AcOH = 1:2:0.05) afforded 12 mg (87%) of **1**: $[\alpha]^{20}_D$ +180.9 (c 0.09, MeOH); FT-IR (thin film, neat) ν_{max} 2926, 1696, 1629 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.0 (br s, 1H), 7.48 (dd, 1H, J = 6.0, 2.6 Hz), 6.96 (d, 1H, J = 11.3 Hz), 6.37 (dd, 1H, J = 6.0, 1.8 Hz), 6.33 (dd, 1H, J = 15.0, 11.4 Hz), 6.25 (dt, 1H, J = 15.0, 7.1 Hz), 5.47 (m, 1H), 5.38 (m, 1H), 3.60 (m, 1H), 2.60 (dt, 1H, J = 14.2, 5.0 Hz), 2.34 (t, 2H, J = 7.4 Hz), 2.33 (m, 1H), 2.23 (q, 2H, J = 7.2 Hz), 2.05 (q, 2H, J = 7.2 Hz), 1.69 (m, 2H), 1.47 (m, 2H), 1.35−1.26 (m, 4H), 0.91 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 178.0, 160.6, 147.0, 135.4, 135.0, 131.8, 131.3, 126.1, 125.6, 43.4, 33.5, 33.1, 31.4, 30.7, 28.4, 26.5, 24.4, 22.5, 14.0; LR-MS (FAB) m/z 317 ($M + H^+$); HR-MS (FAB) calcd for $C_{20}H_{29}O_3$ ($M + H^+$) 317.2117, found 317.2121.

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Supporting Information Available: Characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.