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A new approach to the synthesis of cross-conjugated cyclopentenone prostaglandins. Synthesis of (±)-15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 methyl ester

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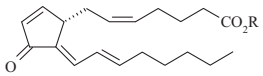
ABSTRACT

A new approach to 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 and related structures based on the (±)-Corey lactone diol has been developed. The key stage of this approach involves building the structure of a prostaglandin (PG) derivative with leaving groups at positions 9, 13, and 15, followed by elimination of these groups by treatment with an organic base.

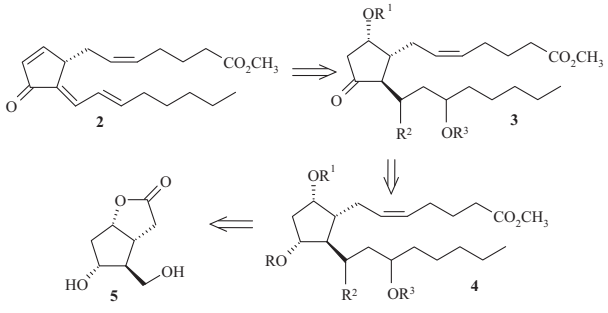
In the series of cyclopentenone prostaglandins (PG),[1] 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**1**),[2] with a cross-conjugated trienone moiety on the ring is of great interest due to its unique mechanism of action[3] and prospects for its practical applications.[4] 15-Deoxy-$\Delta^{12,14}$-PGJ_2 is a selective ligand for PPARγ (peroxisome proliferator-activated receptor γ)—nucleus receptors that directly regulate gene transcription and are responsible for initiation of inflammatory processes, apoptosis, inhibition of virus replication, etc.[4] Many reports on the biological properties of 15-deoxy-$\Delta^{12,14}$-PGJ_2 are available. However, syntheses of compound **1** reported in the literature are quite limited.[5]



1 R = H
2 R = CH_3

In this Letter we describe a new approach to prostaglandin **1** and related structures with the example of the synthesis of the title compound **2**. The key stage of this approach involves the synthesis of orthogonally protected derivatives of F-series prostaglandins, that is, compounds with the general formula **4** in which the protecting group (R) of the C-11 hydroxyl can be selectively removed without affecting the other groups. The protecting groups and substituents R^1, R^2, and R^3 should be chosen from among inherently good leaving groups, such as acetates, tosylates, mesylates, carbonates, etc. In the next stage, ketone **3**, which can be formed by oxidation of the C-11 hydroxyl should undergo stepwise decomposition under the reaction conditions or with the aid of promoters to eventually give the target prostaglandin **2** (Scheme 1).

Standard prostaglandin techniques and synthons were used in a previous synthesis of one representative of compounds **4**.[6] The Corey (±)-lactone diol **5** was used as the starting compound, which was obtained according to a described procedure.[7] The synthesis of key prostaglandin intermediate **14** is shown in Scheme 2. Lactone diol **5** was converted into fully protected lactone **7** by selective



Scheme 1. Retrosynthetic analysis of (±)-**2**.

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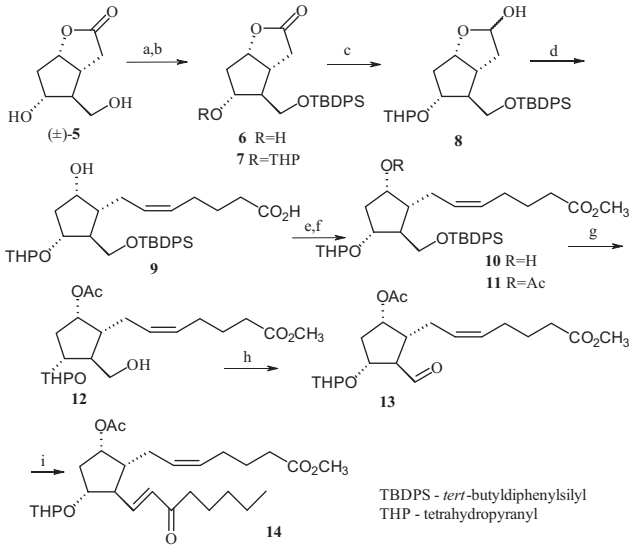
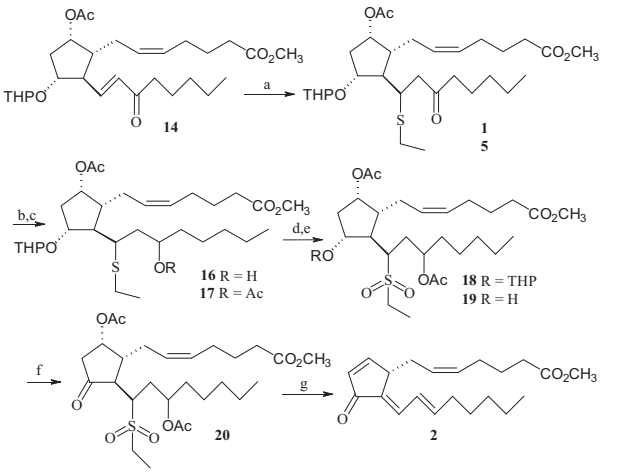


Scheme 2. Reagents and conditions: (a) *t*-BuPh2SiCl (1.2 equiv), imidazole, CH_2Cl_2, 85%; (b) DHP, CH_2Cl_2, PPTS (cat.), 95%; (c) *i*-Bu_2AlH, CH_2Cl_2, −70 °C, 95% (crude); (d) $Br^-Ph_3P^+(CH_2)_4CO_2H$, NaHMDS, THF; (e) CH_2N_2; (75% overall two steps, d and e); (f) Ac_2O, Py, 83%; (g) Bu_4NF, THF, 85%; (h) CrO_3–Py, CH_2Cl_2, 90%; (i) $(MeO)_2P(O)CH_2C(O)C_5H_{11}$, $Et_4N^+Br^-$, NaOH, CH_2Cl_2/H_2O, 80%.

protection of the primary hydroxyl group as a *tert*-butyldiphenylsilyl ether and subsequent blocking of the secondary hydroxyl of **6** with dihydropyran. Reduction of **7** with *i*-Bu_2AlH at −70 °C in CH_2Cl_2 and olefination of unstable lactol **8** with the in situ generated ylide [$Ph_3P{=}CH(CH_2)_3CO_2Na$] led to hydroxyl acid **9**. This was transformed in three steps into alcohol **12**, and then converted into the aldehyde **13**. Emmons–Horner condensation of aldehyde **13** with dimethyl 2-oxo-heptylphosphonate gave the key enone **14**.

In constructing compounds with general formula **4**, enone **14** appears to be a rational building block for introducing the C-13 leaving group by Michael reaction with O-, N-, or S-nucleophiles (Scheme 3). At first, considering that base-catalyzed addition of mercaptans to enones occurs readily, we studied the 1,4-conjugate addition of ethanethiol to enone **14**[8] in THF. This reaction promoted by NaH occurred quickly to give adduct **15** in high yield. The next stage of this work involved the conversion of the substituents and functional groups at C-13 and C-15 in **15** into good leaving groups. As a first approximation, we introduced the sulfone and acetate functions, respectively, at these centers which seemed



Scheme 3. Reagents and conditions: (a) EtSH, THF, NaH, 95%; (b) $NaBH_4$, MeOH, 90%; (c) Ac_2O, Py, 98%; (d) 30% H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}7H_2O$, 73%; (e) 30% AcOH, 60 °C, 82%; (f) PCC, CH_2Cl_2, 86%; (g) DBU, C_6H_6, 20 °C, 32%.

to be the simplest and most convenient approach. Thus adduct **15** was reduced with $NaBH_4$ to give alcohol **16** in high yield. This was acylated and the resulting compound **17** was oxidized with H_2O_2 under catalysis with an Mo(VI) salt to give sulfone **18**. Removal of the THP protecting group in **18**, followed by oxidation of the resulting alcohol **19** with PCC gave ketone **20**. Elimination of the leaving groups in compound **20** under acidic conditions failed. In addition, ketone **20**[8] remained unchanged after refluxing in benzene containing an equivalent amount of benzoic acid for half an hour. However, it was smoothly converted into compound **2**[8] in 32% yield on stirring in benzene with DBU at room temperature. During the reaction minor amounts of by-products were formed which were removed by column chromatography. In particular, ^{1}H NMR analysis of the crude reaction mixture showed the presence of 13,14-*cis*-isomers of **2**, 15α,β-acetate methyl ester 12-PGJ_2 among others, which were not isolated.

Stereochemistries of the *E*,*E*-olefinic double bonds of **2** at C14–15 and C12–13 were confirmed from their coupling constants [$J_{14,15}$ = 14.9 Hz and $J_{13,14}$ = 11.3 Hz ($\delta_{13\text{-H}}$ = 6.96 ppm), respectively], which are consistent with those reported earlier for **1**.[5a,5b] Hence, the methyl ester of (±)-$\Delta^{12,14}$-PGJ_2 **2** has been obtained in 16 steps and 4% overall yield starting from Corey lactone diol **5**. The hydrolysis of the base sensitive ester **2** has been accomplished previously by using lipases and esterases.[9]

In conclusion, the developed method to synthesize compound **2** based on readily available traditional prostaglandin building blocks (Corey lactone diol **5** and 15-oxoprostadienoic acid derivative **14**) can be implemented in the chiral version and can be varied in terms of the analogues that can be obtained.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.096.

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8. *Spectral data for selected compounds: (±)-(3αR*,4S*,5R*,6αS*)-4-({[tert-butyl(diphenyl)silyl]oxy}methyl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one* (***6***): Colorless crystals, mp 95–97 °C; R_f 0.22 (PE–EtOAc, 7:3). IR (KBr) ν_{max} = 3456, 3070, 1749, 1458, 1375, 1357, 1114, 1033, 707 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 6.0 Hz, 4H); 7.45–7.37 (m, 6H); 4.87 (td, *J* = 6.9, 2.9 Hz, 1H), 4.20–4.13 (m, 1H), 3.71 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.61 (dd, *J* = 10.5, 6.7 Hz, 1H), 2.69 (dd, *J* = 17.7, 9.9 Hz, 1H), 2.60–2.55 (m, 1H), 2.42–2.38 (m, 2H), 2.10 (br s, 1H), 2.01–1.95 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 177.20, 135.44, 132.79, 129.90, 127.78, 83.65, 74.95, 64.18, 55.30, 40.54, 39.34, 35.21, 26.80, 19.06 ppm. MS (ESI): *m*/*z* (%): 411 [M+H]$^+$ (20.6), 393 [M–H_2O]$^+$ (5.9), 365 (82.4), 333 [M–PhH]$^+$ (100).
Methyl (±)-(5Z,9α,11α,13E)-9-(acetyloxy)-15-oxo-11-(tetrahydro-2H-pyran-2-yloxy)prosta-5,13-dien-1-oate (***14***): Colorless oil, R_f 0.7 (PE–EtOAc, 1:1). IR (KBr) ν_{max} = 2950 (s), 2934 (s), 1735 (s), 1700 (w), 1680 (w), 1620 (w), 1242 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (m, 1H, C-13–H), 6.18 (dt, *J* = 1.7, 15.9 Hz, 1H, H-14), 5.35–5.20 (m, 2H, CH=CH), 5.00 (br s, 1H, H-9), 4.55 (br s, 0.5H) and 4.50 (br s, 0.5H) (H-1, THP), 4.10–3.90 (m, 2H, H-11, H-5, THP), 3.75–3.65 (m, 1H, H-5, THP), 3.60 (s, 3H, OCH_3), 3.40–3.30 (m, 1H, H-12), 2.75–2.60 (m, 1H), 2.55–2.45 (m, 2.5H), 2.30–2.40 (m, 0.5H), 2.22 (t, *J* = 6.9 Hz, 2H, H-2), 2.15–2.05

(m, 1H), 2.01, 2.00 (s, 3H, OAc), 2.00–1.90 (m, 2H), 1.80–1.40 (m, 10H), 1.35–1.25 (m, 5H), 0.85 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 200.42 and 200.28 (C-15), 173.82 (C-1), 170.53 and 170.43 (OAc), 146.95 (C-13), 131.77 and 131.56 (C-5), 130.03 (C-14), 127.73 and 127.71 (C-6), 99.18 and 96.61 (C-1–THP), 81.02 and 78.78 (C-11), 74.48 and 74.18 (C-9), 62.68 and 61.69 (C-5–THP), 53.54 and 52.99 (C-12), 51.42 (OCH_3), 47.37 and 47.30 (C-8), 40.42 and 40.23 (C-16), 40.12 and 38.47 (C-10), 33.32 (C-8), 31.42 and 31.40 (C-2–THP), 30.66 (C-18), 26.55 (C-4), 25.33 and 25.27 (C-7), 25.07 and 25.02 (C-4–THP), 24.62 (C-3), 23.95 and 23.92 (C-17), 22.43 (C-19), 21.19 and 21.18 (Ac), 19.60 and 19.01 (C-3–THP), 14.14 and 13.88 (CH_3) ppm.

*Methyl (±)-(5Z)-9α,15α,β-bis(acetyloxy)-13α,β-(ethylsulfonyl)-11-oxoprost-5-en-1-oate (**20**):* Colorless oil, R_f 0.3 (PE–EtOAc, 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.45–5.35 (m, 2.5H, CH=CH, H-9), 5.10 (br s, 0.5H, H-9), 4.95–4.85 (m, 1H, H-15), 3.87–3.82 (m, 1H, H-13), 3.65 (s, 3H, OCH_3), 3.10 (dd, J = 7.3, 15.2 Hz, 1H, H-10), 2.98 (dd, J = 7.7, 15.2 Hz, 1H, H-10), 2.50–2.20 (m, 3H), 2.30 (t, J = 6.5 Hz, 2H, H-2), 2.07 s, 2.03 s, 1.98 s (6H, 2OAc), 1.70–1.50 (m, 4H), 1.38 (t, J = 7.5 Hz, 3H, CH_3), 1.30 (br s 7H), 0.85 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 212.76 (C-11), 173.96 and 173.91 (C-1), 171.46, 170.86, 170.56, 170.52 and 170.27 (OAc), 131.42, 130.69 (C-5), 127.18 and 126.17 (C-6), 77.96 and 76.17(C-9), 71.42, 71.35, 70.54 and 70.31 (C-15), 56.30 (C-12), 49.37 and 49.15 (C-13), 46.52 and 46.39 (CH_2SO_2), 45.38 and 43.29 (C-8), 43.31 and 37.75 (C-10), 34.85 and 34.74 (C-16), 33.48 and 33.44 (C-2), 33.13 and 32.74 (C-14), 31.62 and 31.57 (C-18), 26.83 and 26.81 (C-4), 26.64 and 26.59 (C-7), 24.81, 24.76 and 24.71 (C-3, C-17), 22.47 (C-19), 21.31, 21.20, 21.13, 21.07, 21.01 and 20.97 (OAc), 13.98 (CH_3), 6.59 and 6.24 (CH_3) ppm.

*Methyl (±)-(5Z,12E,14E)-11-oxoprosta-5,12,14-trien-1-oate (**2**):* Yellow oil, R_f 0.55 (PE–EOAc, 7:3). IR (KBr) ν_{max} = 2954, 2928, 2856, 1738, 1695, 1634 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (dd, J = 1.9, 6.0 Hz, 1H, H-9), 6.95 (d, J = 11.3 Hz, 1H, H-13), 6.36 (dd, J = 1.8, 6.1 Hz, 1H, H-10), 6.32 (dd, J = 11.4, 15.0 Hz, 1H, H-14), 6.25 (dt, J = 6.9, 14.9 Hz, 1H, H-15), 5.48–5.43 (m, 1H, H-5), 5.39–5.33 (m, 1H, H-6), 3.65 (s, 3H, OCH_3), 3.55–3.60 (m, 1H, H-8), 2.60 (dt, J = 14.5, 6.3 Hz, 1H, H-7), 2.33–2.28 (m, 1H, H-7), 2.28 (t, J = 7.5 Hz, 2H, H-2), 2.23 (q, J = 7.3 Hz, 2H, H-16), 2.20 (q, J = 7.3 Hz, 2H, H-4), 1.65 (quin, J = 7.5 Hz, 2H, H-3), 1.45 (quin, J = 7.2 Hz, 2H, H-17), 1.33 –1.25 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 197.43, 173.94, 160.69, 146.96, 135.38, 135.06, 131.72, 131.50, 125.99, 125.67, 51.56, 43.51, 33.50, 33.43, 31.45, 30.76, 28.50, 26.69, 24.72, 22.51, 14.05 ppm. MS (ESI): m/z (%): 330.3 $[M]^+$ (90), 299 $[M–OCH_3]^+$ (10), 259 $[M–C_5H_{11}]^+$ (100). HRMS (ESI): calcd for $C_{21}H_{30}O_3$: 330.2231, found: 330.2209.

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