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Mendeleev Commun., 2023, **33**, 479–480

Mendeleev Communications

A facile synthesis of (±)-15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 methyl ester

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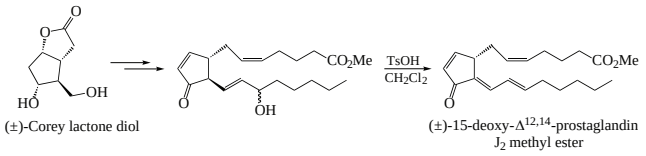
DOI: 10.1016/j.mencom.2023.06.012

A simple and facile synthesis of racemic 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 methyl ester from readily available Corey lactone diol in total eleven steps was suggested. The standard methods provided a pathway to a block with an integrated ω-chain and further to PGJ_2 methyl ester. The latter was smoothly converted to the target prostaglandin in the $TsOH–CH_2Cl_2$ medium when allylic alcohol moiety was transformed to exocyclic diene substituent conjugated with endocyclic enone system.



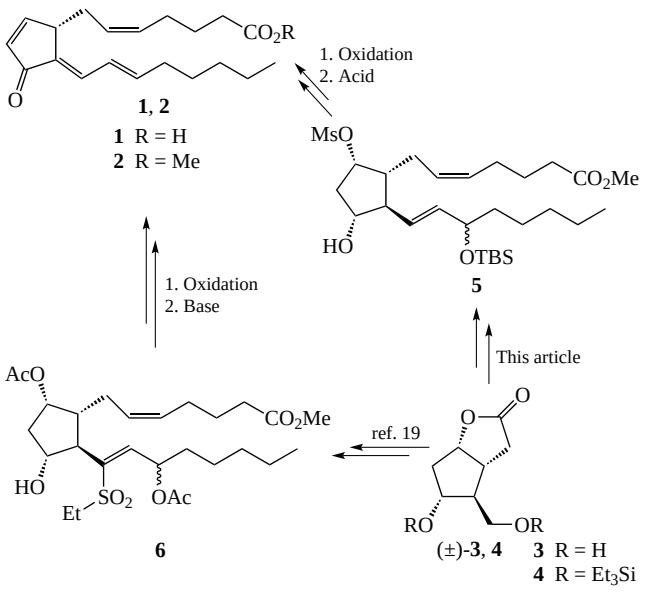
Keywords: Corey lactone diol, prostaglandin J_2 methyl ester, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, diastereoselective reaction, dehydration, dienes.

In the series of prostaglandins (PGs), the cross-conjugated cyclopentenone prostaglandins (cyPG) attract attention due to not only their unique structure but also their bioactivity profile differing from those of the classical PGs.[1] Of the cross-conjugated cyPGs, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15dPGJ$_2$) **1**, a well-known ligand agonist of PPAR$_\gamma$ nucleus receptors responsible, *e.g.*, for gene transcription, apoptosis initiation, viral replication, and inflammatory modulation,[2,3] is the most-studied and popular agent. As a powerful Michael acceptor, highly electrophilic cyPG **1** reacts with the SH groups of nucleus proteins, thereby disrupting their biochemical functions, which is ultimately a predetermining factor in the bioactivity.[4] Note that unlike the majority of proinflammatory prostaglandins, 15dPGJ$_2$ exhibits anti-inflammatory properties.[5]

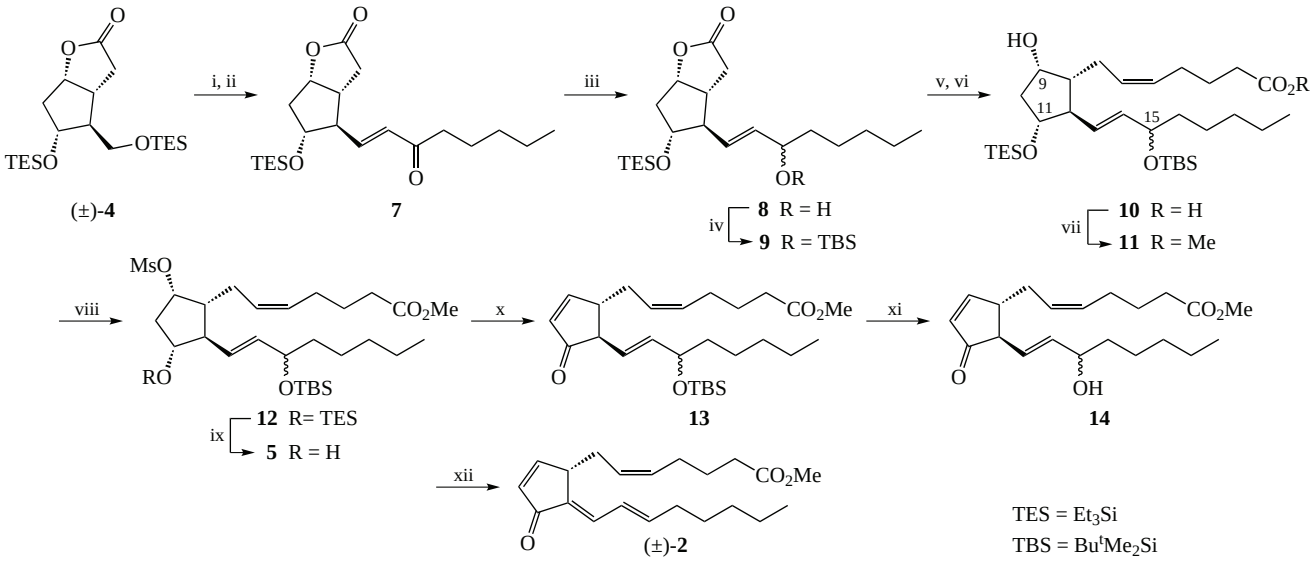
The first synthesis of 15dPGJ$_2$ **1** was performed by Sutton in 2003.[6] In the following years, a number of papers have been published on the synthesis of **1** and its methyl ester **2** as well as their structurally related analogues.[7–16] To a considerable extent, the interest in these compounds was supported by the growing need for biomedical studies.[17,18] We have published two articles[19,20] on this subject. Now we present an improved version of the previously reported[19] approach to compound **2**, the previously obtained[21] (±)-lactone diol **3** serving as the basic starting point in both approaches. The key steps in the approaches involve the transition to differently blocked hydroxy derivatives of compounds **5** and **6**, which give the target substance **2** after oxidation and elimination of the protective groups (Scheme 1).

In continuation of the alternative approach, bis-TES ether **4** (TES is triethylsilyl) was first entered in the sequence of reactions of chemoselective Swern oxidation and Horner–Wadsworth–Emmons olefination with dimethyl 2-oxoheptylphosphonate to give known[22] enone **7** (Scheme 2). Subsequent steps of cerate ($NaBH_4$–$CeCl_3$) reduction of the keto group in enone **7** and TBS-protection of the allylic hydroxy substituent in **8** resulted in lactone **9**. To build the upper chain of PG, lactone **9** was reduced with Bu^i_2AlH to the lactol, which was Wittig-olefinated with the ylide derived from 5-(triphenylphosphonio)pentanoic acid bromide to give the corresponding *Z*-configured olefinic acid **10**. The latter was further converted to methyl ester **11**. After mesylation of the C^9–OH group in **11**, selective hydrolysis of the TES protective group at C^{11} in **12** followed by oxidation of the C^{11}–OH function with diacetoxy(phenyl)iodinane PhI(OAc)$_2$–TEMPO system afforded the PGJ_2 derivative **13**. At the final step, hydrolysis of the silyl protective group in **13** gave PGJ_2 methyl ester **14**, which was smoothly dehydrated to **2** in $TsOH–CH_2Cl_2$ medium.

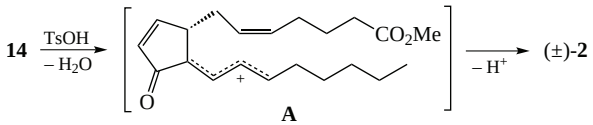
Note that the stereoisomeric purity observed at the generation step (**14** → **2** transition) of the diastereoisomeric system is explained by the reaction pathway through the flat homoallyl carbocation **A** (Scheme 3), which levels off the possible effect of isomerism in the hydroxy-bearing center, to give thermodynamically advantageous *E*,*E*-isomer **2**. Though this aspect is



Scheme 1



Scheme 2 *Reagents and conditions*: i, Swern oxidation; ii, dimethyl 2-oxoheptylphosphonate, NaH, THF; iii, $NaBH_4/CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 89%; iv, TBSCl, ImH, CH_2Cl_2, 86%; v, Bu^i_2AlH, CH_2Cl_2, –78 °C; vi, $Br^-[Ph_3P^+(CH_2)_4COOH]$, NaHMDS, THF, –30 °C; vii, CH_2N_2, Et_2O, 70% (3 steps); viii, MsCl, Et_3N, CH_2Cl_2, 0 °C, 85%; ix, citric acid, THF–H_2O, 85%; x, $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 92%; xi, 40% HF (aq.), MeCN, 80%; xii, TsOH, CH_2Cl_2, 84%. NaHMDS = $Na[N(SiMe_3)_2]$; TEMPO = 2,2,6,6-tetramethylpiperidin-1-yl oxyl.



Scheme 3

obvious, it was not addressed in the syntheses of **1** and **2** reported previously.

In general, the developed approach is based on the use of traditional PG methodologies and reagents. The noteworthy aspects include the **4**→**7** transition by selective oxidation of TMS and TES ethers suggested in the previous work,[22] which allowed a significant reduction in the number of steps from the Corey lactone diol to enone **7**, and the method of selective hydrolysis of the TES ether at C^{11} in the presence of TBS ether at C^{15} in compound **12**. The conditions for the exclusively stereoselective generation of the dienone system in the **14**→**2** transition were found. The suggested scheme of synthesis is simple and suitable for scaling and preparation of non-racemic α- and ω-modified analogues of compounds **1** and **2**.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.012.

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Received: 7th December 2022; Com. 22/7064