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A Carbohydrate Approach to 4-Hydroxy-2-Cyclopentenone Moiety of Antitumor Prostanoid Punaglandin IV *via* Alkylation of Ester Uronate

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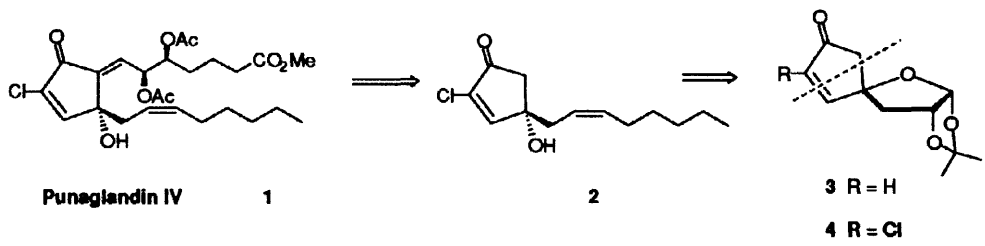
Abstract: An efficient and stereoselective synthesis of a chiral precursor of 2-chloro-4-hydroxy-4-alkyl-2-cyclopentenone has been realized by alkylation of a sugar methyl uronate derived from 1,2-*O*-isopropylidene α-D-glucose with an acetonyl equivalent, and subsequent intramolecular Wittig reaction.

Punaglandin IV **1** belongs to a class of cyclopentenone prostanoids which display a high antitumor activity.[1] Three different syntheses of the intermediate **2** have been described so far, one racemic by Sakai and Shibasaki[2] and the two others, chiral, by Noyori and coll.[3] and Mori and coll.[4] In each case, the strategy adopted is based on a 1,2-addition of organometallic species to a protected 4-hydroxy-2-cyclopentenone. Unfortunately, this reaction suffers from some racemisation of starting material as recently reported by Zwanenburg.[5]

We are engaged in the development of new methodologies for the synthesis of 4-alkyl-4-hydroxy-cyclopentenones as intermediates for new antitumor prostaglandin syntheses. Therefore, we selected the spirofurano cyclopentenone **3** as potential precursor of cyclopentenones **4** and **2**. This latter compound is an intermediate in the Punaglandin IV synthesis.[2-4] Moreover, compound **3**, which could be obtained from D-glucose, could also lead to new antitumor prostanoids by modification of their α and ω side-chains (Scheme 1).



Punaglandin IV **1** **2** **3** R = H **4** R = Cl

Scheme 1

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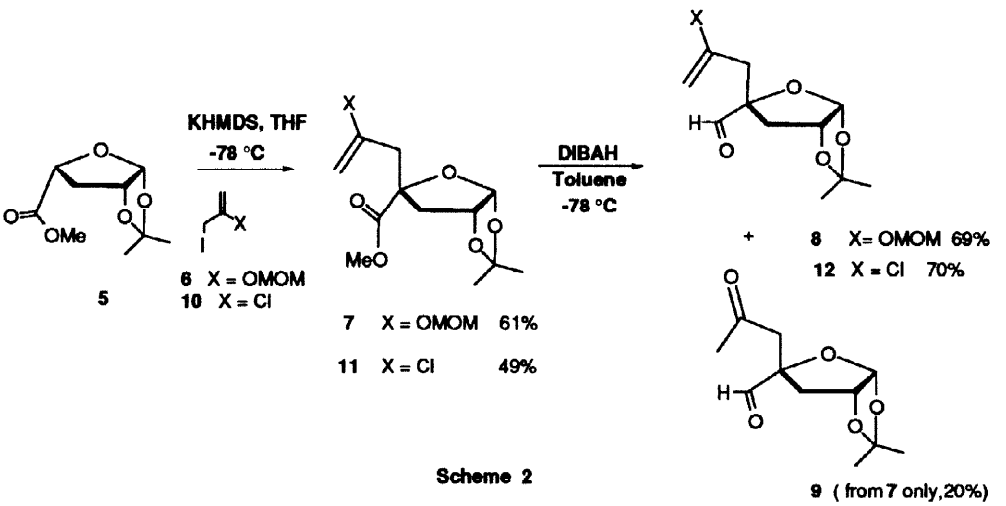
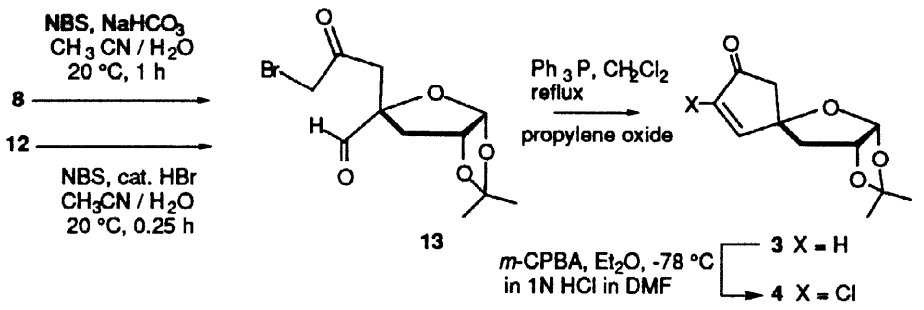
In this way, we previously reported an original one-pot synthesis of cyclopentenone **3** based on a tandem 3-aza-Cope/Mannich reaction occuring during the allylation of an enamino sugar.[6] In spite of its swiftness, this reaction demonstrated a lack of diastereoselectivity for the new stereogenic center formed. Therefore, and as an extension of this work, we examined a new approach based on the alkylation of urono ester **5** with acetonyl equivalents. We had previously shown that, in such reaction, the diastereoselectivity was efficiently controled by the bulky isopropylidene acetal positioned under the plane of the potassium enolate intermediate.[7] After this alkylation, an annelation step should provide the expected cyclopentenone ring.

Under internal quench conditions (electrophile, KHMDS, THF -78 °C) (Scheme 2), treatment of ester **5**, easily prepared from 1,2-isopropylidene D-glucose,[8] with the 2-MOM-1-iodoprop-2-ene **6**[9] as the electrophile, gave compound **7** (61%) with a high diastereoselectivity (e.d. > 95%).



Scheme 2

Once the new quaternary center successfully formed, we focused on the annelation step to built the cyclopentenone ring. Therefore, ester **7** was reduced (DIBAH, toluene -78 °C) to give aldehyde **8** (69%),[10] along with the corresponding methyl ketone **9** (20%) isolated as a side-product. To avoid this problem, we next used the 2-chloro-1-iodo-prop-2-ene **10**[11] as another acetonyl equivalent, which should be potentially more stable under these reducing conditions. Alkylation of ester **5** with **10** gave the ester **11** (49%), which was reduced as above to give the aldehyde **12** in good yield (70%). To promote annelation by an intramolecular ene-reaction between the nucleophilic enol ether and the aldehyde group, we surveyed some Lewis acid catalysts. The use of TMSOTf, $SnCl_4$ or $BF_3{\cdot}Et_2O$ did not furnish the expected product. In consequence, we changed our strategy and decided to realize the ring closure using an intramolecular Wittig reaction (Scheme 3).



Scheme 3

Thus, the 2-substituted allyl side-chains of aldehydes **8** and **12** were transformed into the corresponding α-bromo ketones (for compound **8** with NBS in aqueous MeCN.[12] In the case of **12**, the reaction of NBS with HBr cat.[13] was used. In both cases, as soon as the intermediate α-bromo ketone **13** was obtained, it was directly engaged in the next step and treated with triphenyl phosphine in the presence of propylene oxide as proton scavenger to give the expected spirofurano cyclopentenone **3** in crystalline form.[14] The stereochemistry of the quaternary center was unambiguously confirmed by RX crystallographic analysis. Chlorination of **3** (*m*-CPBA, 1N HCl in DMF)[15] gave the targeted 2-chloro-2-cyclopentenone **4**.

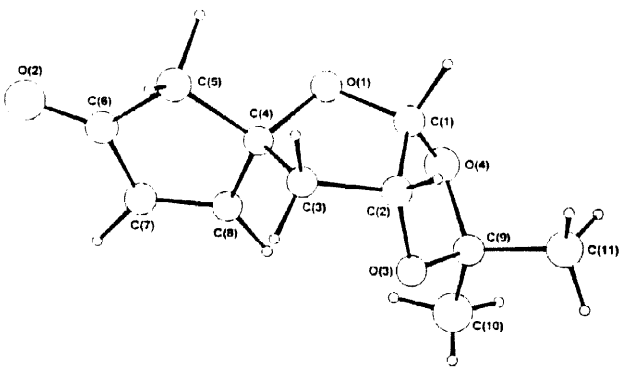


Fig 1. ORTEP diagram of the spirofuranocyclopentenone **3**.[16]

In conclusion, stereocontrolled alkylation of the α-alkoxy ester enolate moiety derived from the uronosugar **5** with an acetonyl equivalent, followed by an intramolecular Wittig reaction, constitutes an efficient way to prepare precursors of chiral 4-alkyl-4-hydroxy-2-cyclopentenone for the synthesis of Punaglandin IV **1** or related analogs. Cleavage of the 1,2 diol obtained after opening of the dioxolane acetal, and subsequent elongation of the side-chain by Wittig olefination are under investigation.

Further extension of this strategy to other ester enolates is being carried on and will be published elsewere.

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10. Data for compound **8** $[\alpha]_D^{20}$-48 (*c* 0.9, $CHCl_3$); IR ($CDCl_3$) ν_{max} (cm^{-1}) 1249 (ether), 1733 (C=O aldehyde), 2956 ($=CH_2$); RMN ^1H (250 MHz, $CDCl_3$) δ 9.85 (s, 1H, CHO), 5.97 (d, 1H, $J_{1,2}$ = 4 Hz, H-1), 4.98 and 4.95 (2d, 2H, AB syst., J = 14 Hz, O-CH_2-O), 4.75 (dd, 1H, $J_{2,1}$ = 4 Hz, $J_{2a,3a}$= 3 Hz, H-2), 4.31 and 4.14 (2d, 2H, AB syst., J = 2 Hz, H-7, H-7'), 3.46 (s, 3H, OMe), 2.86 and 2.45 (2d, 2H, AB syst., J_{gem}= 14 Hz, H-5, H-5'), 2.73 (d, 1H, $J_{3a,3b}$= 14 Hz, H-3b) and 2.05 (dd, 1H, $J_{3a,3b}$ = 14 Hz, $J_{3a,2}$ = 3 Hz, H-3a) , 1.49 (s, 3H, CH_3) and 1.32 (s, 3H, CH_3). MS (DCI/NH_3) *m/z* 290 $[M + NH_4]^+$, 273 $[M + H]^+$.
11. Prepared from 2,3-dichloroprop-1-ene (NaI, in acetone at reflux).
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14. Data for compound **3** $[\alpha]_D^{20}$ -17 (*c* 0.83, $CHCl_3$); mp 68° C; IR ($CDCl_3$) ν_{max} (cm^{-1}) 1680 (C=C), 1723 (C=O).RMN ^1H (250 MHz, $CDCl_3$) δ 7.81 (d, 1H, $J_{8,7}$ = 5.7 Hz, H-8), 6.09 (d, 1H, $J_{7,8}$= 5.7 Hz, H-7), 5.91 (d, 1H, $J_{2,1}$= 4 Hz, H-1), 4.88 (t, 1H, $J_{2,1}$= 4 Hz, $J_{3,2}$= 4 Hz, H-2), 2.76 and 2.46 (2d, 2H, AB syst., J = 18.5 Hz, H-5, H-5'), 2.42 (d, 1H, $J_{3,3'}$= 14 Hz, H-3b) and 2.25 (dd, 1H, $J_{3,3'}$= 14 Hz, $J_{3,2}$= 5 Hz, H-3a), 1.65 (s, 3H, CH_3) and 1.35 (s, 3H, CH_3); MS (DCI/NH_3) *m/z* 228 $[M + NH_4]^+$, 211 $[M + H]^+$. Anal. Calcd. (%) C 62.83, H 6.72. Found (%) C 62.74, H 6.72.
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16. X-ray-structure of compound **3** has been determined at the "Laboratoire de Chimie des Métaux de Transition (Université Paris VI, Mrs. BOIS) with a Enraf CAD4 diffractometer using K_α radiation, 2264 reflexions collected. Crystal system Quadratic, Space group $P4_12_12$, unit cell dimensions (Å) a = 9.602(7), b = 9.610(6), c = 7.3420(10).