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Palladium Catalyzed Syntheses of Phenyl-Substituted $PGF_{2\alpha}$ Analogues: Potential Antiglaucoma Agents

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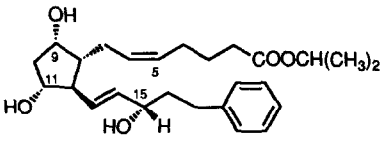
Abstract: *A $PGF_{2\alpha}$-isopropylester derivative with a modified ω-chain containing a phenyl group (1) is an interesting antiglaucoma agent. Herein we describe a synthetic strategy which provides an array of derivatives of 1 by use of palladium catalyzed methods.*

Recently, attention has been focused on prostaglandins, primarily prostaglandin $F_{2\alpha}$ esters, as intraocular pressure (IOP)-lowering substances.[1-3] $PGF_{2\alpha}$-isopropylester significantly reduces IOP,[4,5] but is not suitable for therapeutic use due to side effects such as superficial irritation and vasodilation in the conjunctiva. These side effects are discriminated in $PGF_{2\alpha}$ analogues such as **1** which have a modified ω-chain containing an aryl moiety.[6]

Herein, we report on the syntheses of a series of analogues to **1**. The synthetic strategy is based on medium-scale preparation of key-intermediates **2**[7] which can be conveniently converted into an array of novel derivatives by palladium catalyzed methods.



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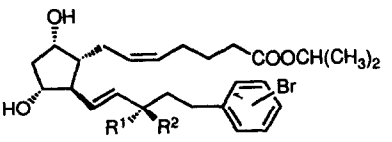


(15S)-**2a**: R^1 = OH, R^2 = H, 4-Br
(15R)-**2a**: R^1 = H, R^2 = OH, 4-Br
(15S)-**2b**: R^1 = OH, R^2 = H, 3-Br
(15R)-**2b**: R^1 = H, R^2 = OH, 3-Br

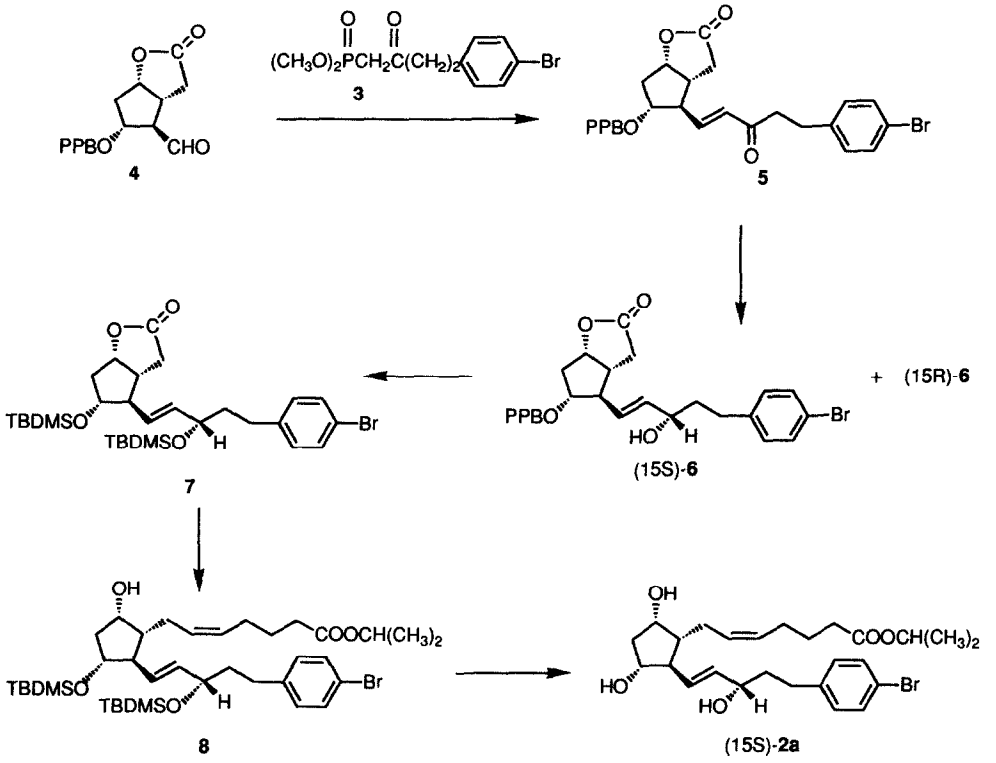
The stereochemically pure epimers of **2** were readily prepared by the same synthetic route which is a modification of Corey's general method.[8] The synthetic route is examplified below with the preparation of (15*S*)-**2a** (Scheme 1): The bromo-substituted phosphonate **3** was synthesized from dimethyl(2-oxopropyl)phosphonate and 4-bromobenzyl bromide (NaH, BuLi, THF; 42 %).[9] Condensation of phosphonate **3** with the oxidized bicyclic lactone **4**[10] [prepared from (1S,5R,6S,7R)-6-hydroxymethyl-7-(4-phenylbenzoyloxy)-2-oxa-bicyclo[3.3.0]octane-3-one (Chinoin) by oxidation with DCC, DMSO and H_3PO_4 in DME][11] under Horner-Emmons conditions[12] furnished **5** (61 %). Non-stereoselective reduction of ketone **5** ($NaBH_4$, $CeCl_4(H_2O)_7$, MeOH/CH_2Cl_2, -78° C, 2 h)[13] provided an epimeric 53:47(HPLC-analysis) mixture of (15*S*)-**6** and (15*R*)-**6**, respectively (73 %). Alternatively, the reduction could be performed in a stereoselective

manner (Li selectride, -120° C; 70 %)[14] to provide predominantly the 15*S*-epimer (40 % de). The epimeric alcohols were readily separated by a combination of flash chromatography (CH_2Cl_2/EtOAc) and crystallization (CH_2Cl_2/hexane).

Removal of the p-phenylbenzoyl protective group of (15*S*)-**6** (K_2CO_2, MeOH; 98 %) followed by protection of the free hydroxyl groups (TBDMS-Cl, DMAP, Et_3N, CH_2Cl_2 ; 84 %) gave **7**. Reduction of the lactone functionality of **7** (DIBAL, THF, -78° C; 81 %)[15] followed by Wittig reaction with 4-carboxybutyl triphenylphosphonium bromide (t-BuOK, THF)[16] afforded an acid which was esterified (*i*-PrI, DBU,[17] acetone; 75 %) to give **8**. Partial migration of a silyl group was observed during the Wittig reaction. On the basis of previous findings,[18] it may be assumed that the silyl group on the 11-hydroxy substituent migrated to the 9-hydroxyl group.

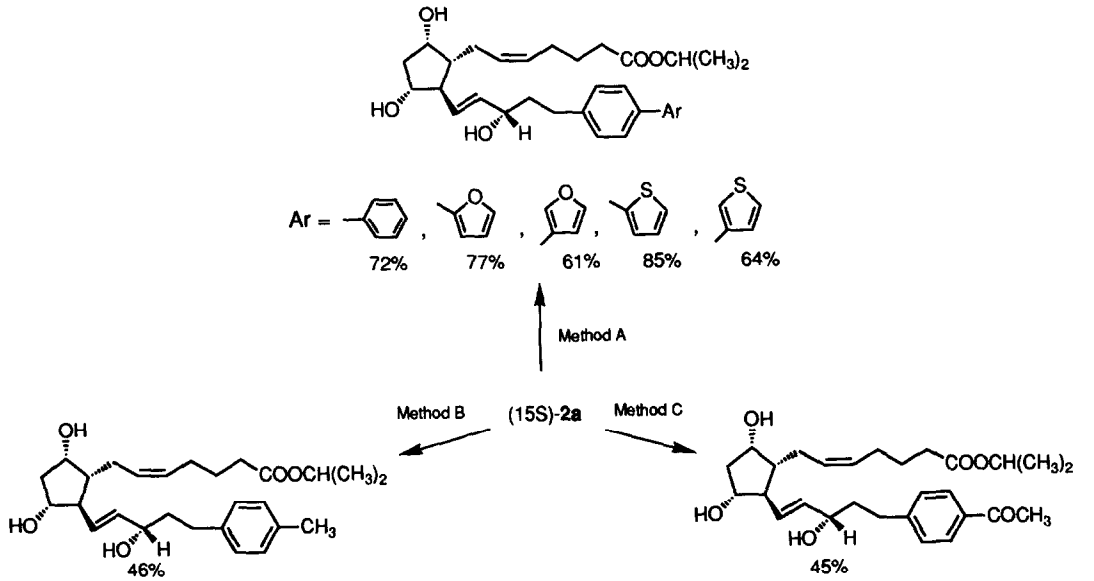
Deprotection of the silylated hydroxyl groups (TBAF, THF; 95 %) gave key intermediate (15*S*)-**2a**. Analytical HPLC[19] showed that the product contained 3 % of the C5-C6 *trans* isomer which was produced during the Wittig reaction. Isomerically pure (15*S*)-**2a** was obtained after purification with preparative HPLC.[20] The isomeric key-intermediates, *i.e.* (15*R*)-**2a**, (15*S*)-**2b** and (15*R*)-**2b**, were obtained under identical conditions and in similar yields.

Scheme 1



Intermediates **2** were converted into potential antiglaucoma agents via three different types of palladium-catalyzed reactions (Methods A-C; Scheme 2). Coupling reactions with a variety of arylboronic acids[21] (Method A; $ArB(OH)_2$, $Pd(PPh_3)_4$, 2M Na_2CO_3, DME/EtOH, 4 h, 95° C) proceeded smoothly and produced the target compounds in good yields (61-90%). The requisite thienyl- and furanylboronic acids were prepared according to facile standard conditions.[22] A modification[23] of the "Stille cross-coupling reaction" was used to introduce methyl groups into **2** (Method B; Me_4Sn, $Pd(OAc)_2$, $P(o\text{-}tolyl)_3$, DMF/Et_3N (4:1), 8 h, 100° C; 45-80 %). The synthesis of acetyl derivatives of **2** turned out to be more difficult than the other reactions. However, Heck reactions[24] of **2** with butyl vinyl ether and hydrolysis of the resulting enol ethers (Method C; (i) Butyl vinyl ether, TlOAc, $Pd(OAc)_2$, $P(Ph)_2(CH_2)_3P(Ph)_2$ (DPPP), DMF, 100 h, 100° C, (ii) aqueous HCl; 40-50 %) produced the desired acetyl derivatives. All these products were purified to homogeneity by preparative HPLC. Only trace amounts of other products were formed during the palladium-catalyzed reactions but isolated yields were moderate since the retention times of the products are similar to that of **2**. The chemoselectivity of palladium catalyzed reactions A-C is noteworthy since we did not observe disturbing side reactions involving the labile allylic alcohol functionality.

Scheme 2.



The $PGF_{2\alpha}$-analogues have been screened in an assay measuring their ability to produce miosis and irritation in the eye (the assay is described in ref 6). Throughout, the analogues cause much less irritation than $PGF_{2\alpha}$ and several derivatives, e.g. (15*S*)-**2b** and the 3- and 4-methyl substituted analogues of (15*S*)-**2**, produce effecive miosis, indicating their potential as antiglaucoma agents. The ability to produce miosis and irritation is stereoselecive since the 15*S*-derivatives appeared to be more potent than the epimers. Results from an ongoing detailed pharmacological evaluation of the compounds will be presented elsewhere.

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7 Physical and spectral data of **2a**: $[\alpha]^{23}_D$ = +25.91° (c 1.03, CH_3CN); mp = 59-61° C; ^1H NMR δ 1.22 (6H, d, H_{23}, $J_{H22,H23}$ = 6.20 Hz), 1.51 (1H, app sept, H_8) 1.65 (2H, app quint, H_3, $J_{H3,H4}$ = 7.02 Hz), 1.75 (2H, m, $H_{10\beta}$ and H_{16a}), 1.85 (1H, m, H_{16b}), 2.05 (3H, m, H_4 and H_{7a}), 2.20 (1H, m, $H_{10\alpha}$), 2.25 (3H, m, H_{7b} and H_2), 2.35 (1H, ddd, H_{12}), 2.62-2.70 (2H, m, H_{17a} and H_{17b}), 3.95 (1H, broad m, H_{11}), 4.10 (1H, ddd, H_{15}, $J_{H15,H16}$ = 6.5 Hz, $J_{H15,H14}$ = 6.5 Hz), 4.185 (1H, broad m, H_9), 4.98 (1H, sept, H_{22}), 5.38 (1H, m, H_5), 5.42 (1H, m, H_6), 5.52 (1H, dd, H_{13}), 5.605 (1H, dd, H_{14}), 7.07 (2H, d, H_{19}), 7.39 (2H, d, H_{20}, $J_{H19,H20}$ = 8.4 Hz); ^{13}C NMR δ 21.84 (C_{23}), 24.88 (C_3), 25.62 (C_7), 26.64 (C_4), 31.21 (C_{17}), 34.02 (C_2), 38.60 (C_{16}), 42.96 (C_{10}), 50.60 (C_8), 55.88 (C_{12}), 67.71 (C_{22}), 71.83 (C_{15}), 73.01 (C_9), 78.21 (C_{11}), 119.53 (C_{21}) 128.91 (C_6), 129.86 (C_5), 130.18 (C_{19}), 131.40 (C_{20}), 132.88 (C_{13}), 134.60 (C_{14}), 140.84 (C_{18}), 173.42 (C_1). Anal. ($C_{26}H_{37}BrO_5$) C, H. All other compounds reported herein also gave spectral data consistent with the assigned structures as well as satisfactory elemental analyses.

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19 Stationary phase: Nucleosil C_{18}, 7 μm, 250 x 4 mm. Mobile phase: phosphate buffer pH 2.5/ acetonitrile gradient, 1.8 ml/min. Detection: 200 nm.

20 Stationary phase: silica gel, 21.4 x 250 mm. Mobile phase: 5-10% etanol in hexane, 15 ml/min. Detection: 220 nm.

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