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Synthesis of New Prostaglandin $F_{2\alpha}$ Derivatives

Chang-Young Oh, Myung-Hee Chun and Won-Hun Ham*

College of Pharmacy, Sung Kyun Kwan University, Suwon 440-746, Korea

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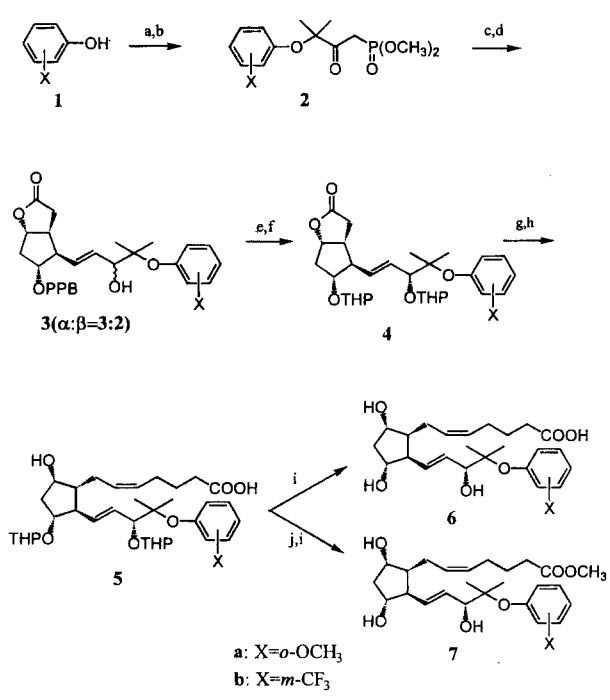
Prostaglandins (PGs) are naturally occuring substances found in animals and men and biosynthesized from C_{20} polyunsaturated fatty acids *via* a cyclooxygenase enzyme system widely distributed in mammalian tissues. PGs were discovered in the 1930s by Von Euler but not until 1957 were they isolated and their structures determined (Bindra, *et al.*, 1977). They play a vital role in the processes of inflammation, tissue repair, and immune response (Samuelsson *et al.*, 1983~1989). Given their enormous potential therapeutic benefits, extensive efforts have been directed toward the design and synthesis of pharmacologically useful analogues.

By the mid-1960s, there was widespread belief that PGs would be useful therapeutic agents in a large mumber of diseases and efforts to synthesize natural compounds and structurally modified analogues became intense in both academic and industrial laboratories. With the progress being made in our understanding of their pharmacological importance, several natural prostaglandins and their analogues are already available on the market for therapeutic usages (Collins *et al.*, 1993). The road to therapeutic utility, however, was impeded by three major problems with natural PGs: (1) chemical instability, (2) rapid metabolism, and (3) incidence of numerous side effects (Collins *et al.*, 1986). The major metabolism of PGs, in order to rapidity, are oxidation of the 15-hydroxy group to a ketone, β-oxidation of the α-chain (upper side chain) to generate acetic acid and the dinor PG acid and ω-oxidation at C-20 to produce the 20-hydroxy and carboxylic acid analogues. The products of these metabolic pathways are all biologically inert.

Recent studies in our laboratories have focused on the stabilization of methyl groups at the carbon 16 of PGs to block the metabolic oxidation of the 15-hydroxy group (Kawada *et al.*, 1989; Ham *et al.*, 1992). In addition, efforts to prevent ω-oxidation at C-20 and, hopefully, induce crystallinity, 16-phenoxy prostaglandin analogues bearing methoxy or trifluoromethyl groups in aryl ring were prepared.



Scheme 1. Reagents and conditions: a) $BrC(CH_3)_2COOC_2H_5$, K_2CO_3, acetone, 45% for **a;** 43% for **b,** b) $CH_3PO(OCH_3)_2$, n-BuLi, THF, 99% for **a;** 97% for **b,** c) Corey aldehyde, NaH, THF, 70% for **a;** 69% for **b,** d) diisobutylaluminium 2,6-di-tert-4-methyl phenoxide, toluene, 84% for **a;** 85% for **b,** e) K_2CO_3, MeOH, 98% for **a;** 97% for **b,** f) DHP, PPTS, CH_2Cl_2, 95% for **a;** 96% for **b,** g) DIBAL, toluene, 90% for **a;** 89% for **b,** h) $Ph_3P{=}CH(CH_2)_3COO^-$, DMSO, 70% for **a;** 68% for **b,** i) $AcOH:H_2O:THF$ (20:10:3), 90% for **a;** 92% for **b,** j) CH_2N_2, ether, 70% for **a;** 72% for **b**

As shown in scheme 1, we completed a straightforward synthesis of **6a,b** and **7a,b** from *o*-guaiacol (**1a**) or α,α,α-trifluoromethyl-*m*-cresol(**1b**) by using the Corey synthesis (Corey *et al.*, 1969).

Treatment of phenols **1a** or **1b** with ethyl 2-bromo-2-methylpropionate and potassium carbonate afforded the corresponding esters, which were reacted with dimethy methyl-phosphonate and n-BuLi at -78°C to give **2a** or **2b**, respectively. The resulting phosphonates **2a** or **2b** were reacted with the Corey's aldehyde in the presence of NaH in THF to give the enones which were reacted with diisobutylaluminium 2,6-*t*-butyl-4-methyl phenoxide (Iguchi *et al.*, 1979) to give a 3:2 mixture of α-isomer and β-isomer in favor of α-isomer as the desired isomer (**3a** and **3b** gave the same ratio). Deprotection of PPB group from α-isomers of **3a**

Correspondence to: Won-Hun Ham, College of Pharmacy, Sung Kyun Kwan University, Suwon 440-746, Korea

or **3b** was achieved with potassium carbonate at R.T. to give the corresponding alcohols, followed by THP protection afforded the desired compounds **4a** or **4b**.

Reduction of **4a** or **4b** with diisobutylaluminium hydride (DIBALH) at -78°C gave the lactols, which without purification underwent the Wittig reaction with the reagent derived from (4-carboxybutyl)triphenylphosphonium bromide in the presence of NaH and DMSO at R.T. to give **5a** or **5b**. Removal of the protecting groups of **5a** or **5b** using aqueous acetic acid afforded **6a** or **6b**. Esterification of **5a** or **5b** with diazomethane followed by treatment with aqueous acetic acid gave **7a** or **7b**.

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