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Synthesis of the highly potent prostanoid FP receptor agonist, AFP-168: a novel 15-deoxy-15,15-difluoroprostaglandin $F_{2\alpha}$ derivative

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Abstract—A novel 15-deoxy-15,15-difluoro-prostaglandin(PG)$F_{2\alpha}$ derivative **6** (AFP-168) has been synthesized from the Corey aldehyde in six steps. A key aspect of this route is difluorination of an enone and a stereoselective Wittig reaction. The compound shows high affinity to the FP receptor and potent activities for an anti-glaucoma agent.
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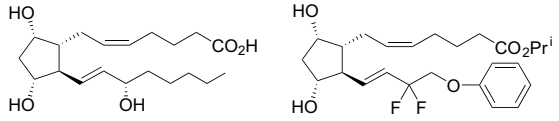
Fluorine has unique physical properties such as a small atomic size, strong electron negativity, and high carbon–fluorine bond energy.[1] Introduction of fluorine atoms into a variety of biologically important substances, for instance steroids,[2] amino acids and peptides,[3] and nucleosides,[4] often brought significant improvement in their pharmacological profiles. A series of prostaglandin (PG) derivatives are particularly attractive targets for us because of their pharmacological importance and a broad range of therapeutic applicability as medicines.[5] Recent advance in molecular biology unveils novel physiological functions of PG receptors.[6] According to cDNA cloning and structural elucidation of PG receptors, exploration research of new PG receptor agonists can be largely accelerated.

Glaucoma is one of the most common, but serious eye diseases that can lead to optic nerve damage and result in blindness if not appropriately treated. A main risk factor is thought to be elevated intraocular pressure (IOP). Since the discovery that $PGF_{2\alpha}$ reduces IOP in an animal model,[7] extensive efforts have been dedicated to develop PGF receptor (FP) agonists as a new anti-glaucoma agent.[8] We have been studied various fluorinated PG derivatives for many years,[9] and we recently found 15-deoxy-15,15-difluoro-$PGF_{2\alpha}$ shows highly potent affinity to the prostanoid FP receptor (Fig. 1).[10,11] We herein report the synthesis of a novel 15-deoxy-15,15-difluoro-$PGF_{2\alpha}$ derivative, AFP-168.



Prostaglandin $F_{2\alpha}$ AFP-168

Figure 1.

A synthetic route for AFP-168 is shown in Scheme 1. The synthesis was started from the Corey aldehyde **1**,[12] which was converted to enone **3** by Horner–Emmons reaction with phosphonate **2** according to the known procedure.[13] Although a geminal difluoride unit has been drawn more attention recently in medicinal chemistry, there is no general method to prepare allyl difluoride from the corresponding enone efficiently.[14] We studied the reaction and found that the fluorination reaction of enone **3** with morpholinosulfur trifluoride[15] in chloroform at 30–40 °C for 82 h and successive deprotection of the benzoyl group with potassium carbonate in MeOH gave geminal difluoride **4** in 71% yield. Reduction of lactone **4** with diisobutylaluminum

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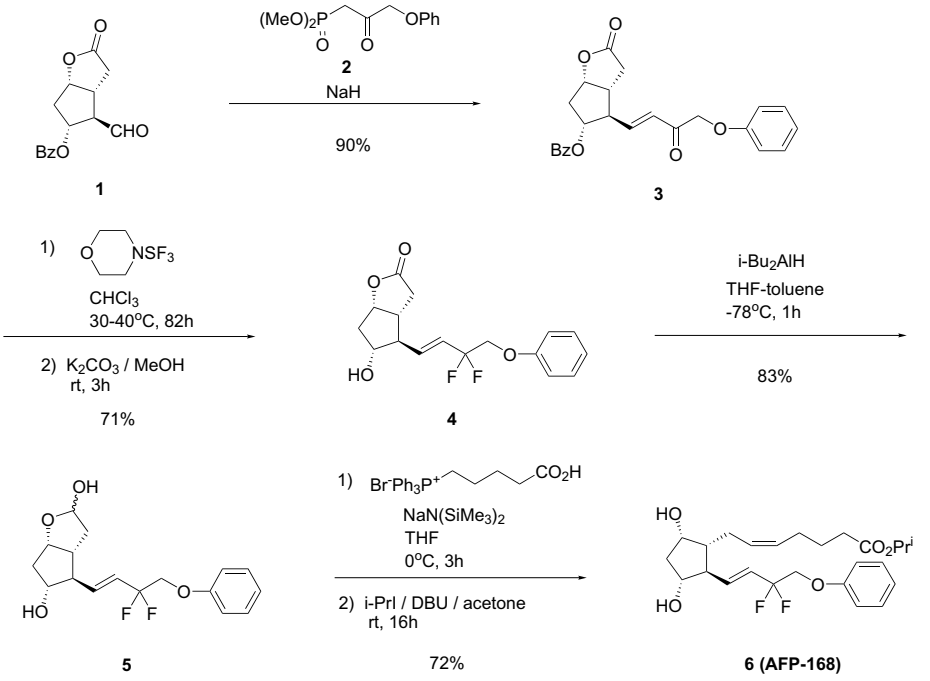

Scheme 1.

hydride in THF–toluene at −78 °C afforded lactol **5** in 83% yield.

The Wittig reaction of lactol **5** with the ylide prepared from 4-carboxybutyltriphenylphosphonium bromide with various bases yielded the 15-deoxy-15,15-difluoro-$PGF_{2\alpha}$ derivative as a mixture of 5*Z* and 5*E* isomers. Reactions using potassium bis(trimethylsilyl)amide or sodium bis(trimethylsilyl)amide as the base gave better yields than the one using dimsyl sodium or *t*-BuOK. When using sodium bis(trimethylsilyl)amide in tetrahydrofuran at 0 °C, the *Z*/*E* stereoselectivity of the reaction was 99:1. The Wittig reaction and successive esterification of the crude acid treated with isopropyl iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetone afforded the desired 15-deoxy-15,15-difluoro-$PGF_{2\alpha}$ isopropyl ester **6** (AFP-168) in 72% yield.[16]

The affinity for the FP receptor of the corresponding carboxylic acid of AFP-168 was 0.4 nM,[10] which was more than 10 times higher than those of latanoprost.[8b] It should be noted that the substitution of a hydroxyl group at 15-position of $PGF_{2\alpha}$ by this novel 15,15-difluoro moiety maintains an inherent nature to bind to the PG receptor with such a higher affinity, although the hydroxyl group had been thought to be necessary to show their pharmacological activities.[5] AFP-168 has a potent IOP reducing effect in animal models and proceeds to clinical trial.

In summary, we synthesized a novel 15-deoxy-15,15-difluoro-$PGF_{2\alpha}$ derivative **6** (AFP-168) from the Corey aldehyde in six steps. The compound shows high affinity to the FP receptor and potent activities for an antiglaucoma agent.

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16. **6**: IR (neat) 3416, 2979, 2934, 1726, 1677, 1497, 1249 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, $J = 6.2$ Hz, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 1.58–1.63 (m, 1H), 1.63–1.69 (m, 2H), 1.84 (d, $J = 14.7$ Hz, 1H), 2.02–2.08 (m, 1H), 2.10–2.16 (m, 3H), 2.25 (t, $J = 7.3$ Hz, 1H), 2.26 (t, $J = 7.1$ Hz, 1H), 2.30–2.35 (m, 1H), 2.46–2.49 (m, 2H), 2.61–2.63 (m, 1H), 4.02–4.03 (m, 1H), 4.18–4.21 (m, 3H), 5.00 (heptet, $J = 6.2$ Hz, 1H), 5.35–5.42 (m, 2H), 5.80 (dt, $J = 15.8$, 11.2 Hz, 1H), 6.10 (dd, $J = 15.8$, 8.8 Hz, 1H), 6.91 (d, $J = 8.8$ Hz, 2H), 7.00 (t, $J = 7.3$ Hz, 1H), 7.30 (dd, $J = 8.8$, 7.3 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −102.8 (dq, $^2J_{FF} = 255.6$ Hz), −103.6 (dq, $^2J_{FF} = 255.6$ Hz). Anal. Calcd for $C_{25}H_{34}F_2O_5$: C, 66.35; H, 7.57. Found: C, 65.99; H, 7.69.