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SHORT SYNTHESIS OF 6-OXOPROSTAGLANDIN E_1 AND 6-OXOPROSTAGLANDIN $F_{1\alpha}$[1]

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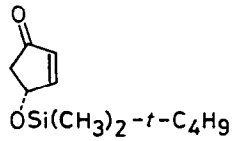
Summary: 6-Oxoprostaglandin E_1 methyl ester was synthesized in a single pot from (R)-4-t-butyldimethylsiloxy-2-cyclopentenone by organocopper conjugate addition with an ω side-chain unit, trapping of the resulting enolate with 6-methoxycarbonyl-2-nitrohex-1-ene, and treatment with aqueous titanium(III) trichloride. Hydrolysis of the methyl ester was accomplished by porcine liver esterase. 6-Oxoprostaglandin $F_{1\alpha}$ was obtained from 6-nitroprostaglandin E_1 methyl ester in four steps.

6-Oxoprostaglandin E_1 (6-oxo-PGE_1, 7), an active metabolite[2] of PGI_2, is known to be one of the most powerful vaso-active metabolites[3,4] in arachidonic acid cascade. On the other hand, 6-oxo-$PGF_{1\alpha}$ (12) is an inactive metabolite derived from PGI_2 by hydration and, consequently, is a useful compound as a diagnostic parameter[5] representing the concentration of PGI_2 under physiological conditions. 6-Oxo-PGE_1 (7) has so far been synthesized only from PGI_2 via oxidation[6] of a 6-oxo-$PGF_{1\alpha}$ derivative.[7] Reported herein is the direct, de novo synthesis of these two 6-oxo-PGs.

In the course of exploring the short way to PGE_1[8] via the three-component coupling process,[9] we have been prompted to find a facile entry to 6-oxo-PGE_1 (7). On the basis of dissection of the 1,4-diketone structure 7, coupled with the characteristic of our synthetic strategy,[8,9] conversion of the nitronate intermediate 4 should be one of the most promising ways leading to the oxo derivative. The generation of the anion 4 could be achieved by the combination of the optically active cyclopentenone block 1[9a,10] and the ω side-chain unit 2 via the organocopper conjugate addition, followed by Michael trapping of the resulting enolate by the nitro-olefin 3.[8] The Nef reaction conditions[11] would be among the most appropriate for the conversion of the anionic intermediate to the oxo compound, thereby realizing a single-pot construction of the PG skeleton which possesses the desired oxidation states.

The vinyl copper reagent[12a,b] was prepared by treatment of the vinylic iodide 2,[13] $[\alpha]_D^{21}$ -30.6° (c 1.57, CCl_4), with 2 equiv of t-butyllithium in ether at -78 °C for 2 h followed by addition of an ethereal solution of copper(I) iodide[12c] (1 equiv) and tributylphosphine (2 equiv). Reaction of the vinylcopper reagent with 0.77 equiv of the enone 1, $[\alpha]_D^{22}$ +63.2° (c 1.04, CH_3OH, 94.3% ee[14]), at -78 °C for 15 min and then at -40 °C for 30 min, followed by treatment with 0.77 equiv of the nitro-olefin 3 at -40 °C for 30 min. Exposure of the mixture to aqueous THF solution of titanium(III) trichloride (12 equiv) and ammonium acetate (72 equiv) at room temperature for 18 h gave the 6-oxo-PGE_1 derivative 5[15] in 66% isolated yield, $[\alpha]_D^{22}$ -39.3° (c



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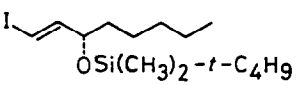

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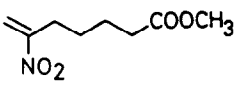

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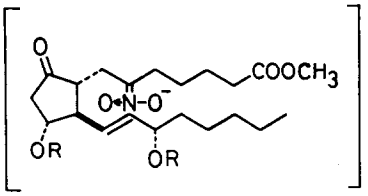
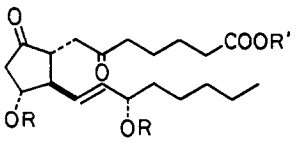


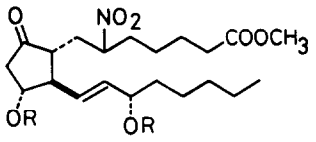
4, R = $Si(CH_3)_2$-*t*-C_4H_9



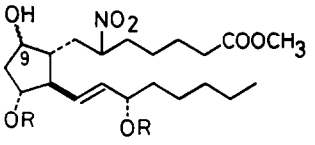
5, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = CH_3

6, R = H; R' = CH_3

7, R = R' = H

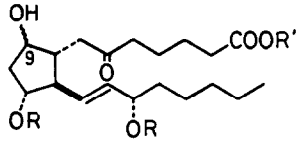


8, R = $Si(CH_3)_2$-*t*-C_4H_9



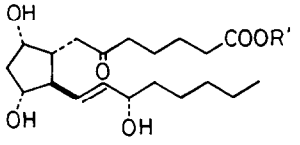
9a, 9α-OH; R = $Si(CH_3)_2$-*t*-C_4H_9

9b, 9β-OH; R = $Si(CH_3)_2$-*t*-C_4H_9



10a, 9α-OH; R = $Si(CH_3)_2$-*t*-C_4H_9; R' = CH_3

10b, 9β-OH; R = $Si(CH_3)_2$-*t*-C_4H_9; R' = CH_3



11, R' = CH_3

12, R' = H

1.04, CH_3OH). In addition, the C-8 epimer, $[\alpha]_D^{22}$ +28° (c 0.55, CH_3OH), was obtained in 10% yield.[16] This was epimerized easily to 5 on a silica gel TLC plate. Desilylation of 5 with hydrogen fluoride–pyridine in acetonitrile (room temp, 3 h) produced 6-oxo-PGE_1 methyl ester (6)[15] (92%), $[\alpha]_D^{21}$ -48.5° (c 0.71, CH_3OH), mp 44.0–44.5 °C (recrystallized from hexane–ether, lit.[7a] mp 39–40 °C). Hydrolysis of 6 with porcine liver esterase[17] (room temp, 18 h) completed the synthesis of naturally occurring 6-oxo-PGE_1 (7)[15] (89% yield), $[\alpha]_D^{20}$ -50.0° (c 1.55, CH_3OH), mp 65 °C (recrystallized from hexane–ether, lit.[7a] mp 67–69 °C). Thus conversion of the *in situ* generated nitronate intermediate 4 into the oxo compound 5 worked quite smoothly. However, attempted nitro to oxo conversion using the neutral 6-nitro compound 8 (a mixture of C-6 epimers)[8] under the original or modified Nef reaction conditions[11] did not meet with great success because of the instability of the oxygenated cyclopentanone moiety. The desired 6-oxo compound 5 was obtaind only by treatment with the combination of triphenylphosphine and buffered titanium(III) trichloride[11b] at room temperature for 5 h (16% yield).

6-Oxo-$PGF_{1\alpha}$ (12) was synthesized from the protected 6-nitro-PGE_1 (8)[8] by the following four-step procedure. Reduction of 8 with diisobutylaluminum 2,6-di-t-butyl-4-methylphenoxide[18] (5 equiv) in toluene at -78 °C for 3.5 h gave a mixture of the 9α alcohol, 9a, and its 9β isomer, 9b, in 80% yield (9a:9b = 7:1). The nitronate intermediate formed by exposure of the mixture to 1 equiv of sodium methoxide in methanol at 0 °C for 3 min was treated with a mixture of 10 equiv of titanium(III) trichloride and 60 equiv of ammonium acetate in aqueous THF[11b] at room temperature for 18 h to give, after silica gel chromatography, the corresponding 6-oxo alcohols, 10a (63%), $[\alpha]_D^{20}$ -10° (c 2.48, CH_3OH), and 10b (9%), $[\alpha]_D^{20}$ -3.5° (c 0.96, CH_3OH). Removal of the silyl groups from 10a with hydrogen fluoride–pyridine (room temp, 1 h) provided 6-oxo-$PGF_{1\alpha}$ methyl ester (11)[15] (96%), $[\alpha]_D^{22}$ +8.2° (c 2.9, CH_3OH). Hydrolysis of 11 with 5N sodium hydroxide in methanol at 40 °C for 3 h afforded 6-oxo-$PGF_{1\alpha}$ (12)[15] (84%), $[\alpha]_D^{21}$ -9.6° (c 1.04, CH_3OH).

Thus the present procedure provides very short syntheses of 6-oxo-PGE_1 and -$PGF_{1\alpha}$ not *via* PGI_2 derivatives. In addition, this recipe gives us an alternative way[19] for direct synthesis of 1,4-dicarbonyl compounds starting from α,β-unsaturated enones and nitro-olefins.

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