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A FACILE SYNTHESIS OF 6-OXO-$PGF_{1\alpha}$ AND 6-OXO-PGE_1[1)]

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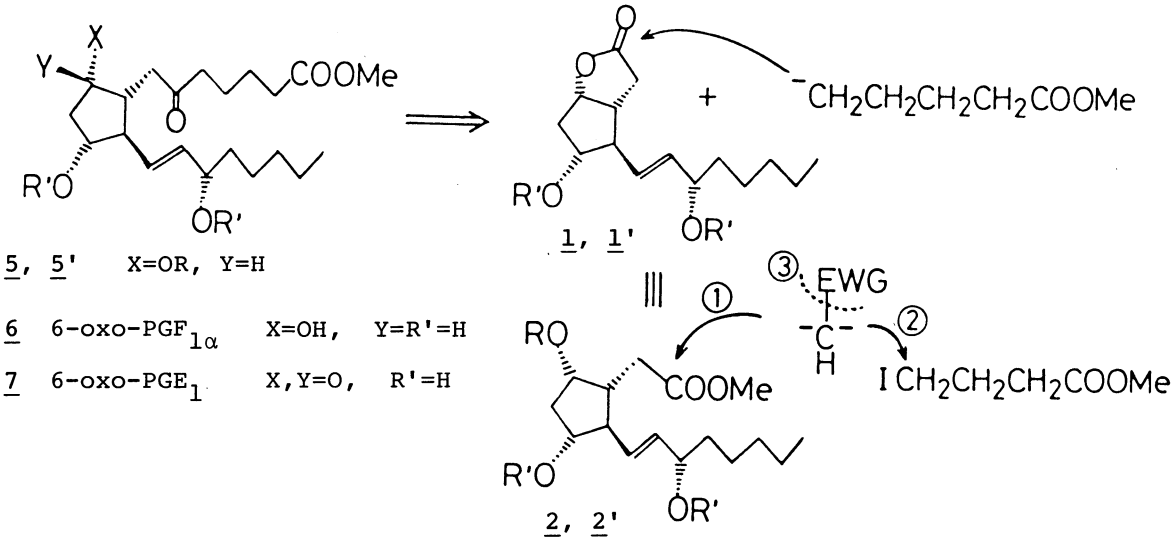
6-Oxo-$PGF_{1\alpha}$ and 6-oxo-PGE_1 were synthesized from 7-t-butyldimethylsililoxy-6-[(1E)-3-t-butyldimethylsililoxy-1-octenyl]-2-oxabicyclo[3.3.0]octan-2-one (1) and 7-tetrahydropyranyloxy-6-[(1E)-3-tetrahydropyranyloxy-1-octenyl]-2-oxabicyclo[3.3.0]octan-2-one (1') via C_5 unit elongation to the lactone carbonyl of 1 and 1' respectively. The C_5 unit was introduced step by step (C_1 + C_4) by means of the conversion of 1 and 1' to the corresponding β-keto esters and then the alkylation of the active methylene of them.

6-Oxo-PGE_1 (7) is one of the most attractive target in prostaglandin (PG) synthesis, because of its higher vaso-activities and availabilities.[2)] There are a few reports on the synthetic study, e.g., syntheses of 6-oxo-$PGF_{1\alpha}$ (6) and 7 via the 6-nitro-PGE_1 derivative by Noyori et al.,[3)] conversion of $PGF_{2\alpha}$ to 6 by Johnson et al.,[4)] and conversion of 6-oxo-$PGF_{1\alpha}$ 11,15-ditetrahydropyranyl ether (5', R=H) to 7 by Nicolaou et al.[5)]

Our strategy for the synthesis of 6-oxo-PGs is to build the 6-oxo ester functionality by joining the C_5 unit (C^1-C^5 part, PG numbering) to lactones 1 and 1'. Because, the lactones are easily available[6)] as an important intermediate for $PGF_{2\alpha}$ synthesis. However, it is well known that there is no suitable method to



1, 2, and 5; R'=R=$SiMe_2Bu^t$, 1', 2', and 5'; R'=THP, R=$SiMe_2Bu^t$

Scheme 1.

introduce directly the C_5 unit into the lactones. We wish to report here a good method to build the C_5 unit step by step (C_1 + C_4) as shown in Scheme 1 (①, ②, and ③).

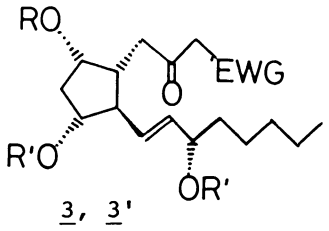
6-Oxo-$PGF_{1\alpha}$ was synthesized as follows. Lactone 1 was hydrolyzed with alcoholic potassium hydroxide, and the resulting salt was washed with hexane and dried well under reduced pressure to give a white powder. To a stirred solution of the salt in dimethylformamide (DMF) was added iodomethane (1.5 equiv.), and the stirring was continued for 1 h at r.t. Imidazole (4 equiv.) and t-butyldimethylchlorosilane (2 equiv.) were successively added to the reaction mixture, and the stirring was continued for additional 10 h to give methyl ester 2 (90% yield after column chromatography on silica gel). The ester 2 was converted to ketones 3a-d, which have an electron-withdrowing group (EWG) attaching active methylene group, by the reaction with the corresponding carbanion as shown in Table 1.[7)]

Table 1. Reaction of Ester 2 (1 mmol) with Carbanion to Ketone 3

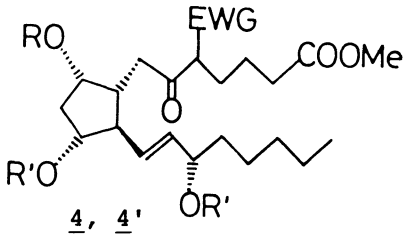
Formation of Carbanion					Reaction with 2			Product 3
CH_3-EWG (mmol)	LDA (mmol)	Temp °C	Time h	Solvent (ml)	Method[a)]	Temp °C	Time h	Yield/%[b)] EWG=
CH_3SCH_3 (12.5)	2.5	0	0.5	THF (5)	A	0	1.0	$-\overset{\overset{O}{\|}}{S}CH_3$ 3a 86
$PhSCH_2COOH$ (2.5)	5.0	0	1.0	THF (4)	A	0-r.t.	2.5	-SPh 3b 71
CH_3COOBu^t (1.0)	2.5	-40	0.5	THF-hexane (2) (2)	B	30	1.5	$-COOBu^t$ 3c 81
					B	-40	1.5	3c 27[c)]
					B	0	0.5	3c 61[d)]
					B	r.t.	0.5	3c 67[e)]
CH_3COOEt (1.0)	2.5	-40	0.5	THF-hexane (2) (2)	B	30	0.5	-COOEt 3d 81[f)]

a) A: Ester 2 was added to the carbanion.
B: The carbanion was added to a solution of ester 2 in THF (1 ml).
b) Isolated yield based on 2.
c) Alcohol ($-\overset{|}{\underset{|}{C}}(OH)(CH_2COOBu^t)_2$, 5%) and 2 (65%) were isolated.
d) Ester 2 (27%) was recovered.
e) β,δ-Diketo ester ($-COCH_2COCH_2COOBu^t$, 3%) and 2 (23%) were isolated.
f) Ester 2 (13%) was recovered.

Alkylation of ketones 3a-d to 4a-d was carried out by treatment with base and methyl 4-iodobutyrate as shown in Table 2. 6-Oxo-$PGF_{1\alpha}$ tri-t-butyldimethylsilil



3, 3'



4, 4'

3 and 4
R'=R=$SiMe_2Bu^t$

3' and 4'
R'=THP, R=$SiMe_2Bu^t$

ether (5) was obtained by desulfurization of 4a (70% yield, excess Al(Hg)) or deethoxycarbonylation of 4d (93% yield, alkaline hydrolysis, decarboxylation, and esterification (diazomethane)), though the conversion of 4b and 4c to 5 was not successful by the usual manner.[8] Deprotection of 5 to 6 was achieved by treatment with tetrabutylammonium fluoride in dry THF at r.t. (90% yield).

Table 2. Alkylation of Ketones 3 to 4

3 EWG=		Base (mol equiv.)	Solvent	Temp °C	Time h	4	Yield/%
3a	$-\overset{\overset{O}{\|}}{S}CH_3$	K_2CO_3 (2)	DMF	r.t.	48	4a	65
3b	-SPh	NaH (1.1)	DMSO-DME	0	1	4b	66
3c	$-COOBu^t$	K_2CO_3 (2)	DME	30	72	4c	62[a]
3d	-COOEt	K_2CO_3 (2)	DME	30	48	4d	93[b]

a) Ketone 3c (36%) was recovered.
b) Methyl 4-iodobutyrate was used in excess (ca. 2 equiv.).

In the case of the synthesis of 6-oxo-PGE_1, a selective oxidation of 6 to 7 is impossible without the protection of 11,15-dihydroxy groups of 6. Therefore, we adopted the method via β-keto ethyl ester 3d' from lactone 1'.
To a stirring solution of 2' (1 mmol), derived from 1' similarly as described in the case of 1 to 2, in THF (1 ml) at 30 °C was added a solution of lithium enolate prepared at -40 °C by addition of ethyl acetate (1 mmol) to lithium diisopropylamide (LDA, 2.5 mmol) in THF-hexane (50% v/v, 4 ml). The stirring was continued for 1.5 h at that temperature to afford β-keto ester 3d' (EWG=COOEt, 80% yield) which was characterized by means of ^1H NMR δ 3.40 (2H, s, $-COCH_2COOEt$) and IR (neat) 1740 (ester), 1715 (ketone) cm^{-1}. The ester 3d' (1 mmol) was treated with K_2CO_3 (2 mmol) and methyl 4-iodobutyrate (2.5 mmol) in 1,2-dimethoxyethane (DME, 2 ml) to give selectively the α-monoalkylated β-keto ester 4d' (EWG=COOEt) in 90% yield: ^1H NMR δ 3.65 (3H, s, $-COOCH_3$); IR (neat) 1735, 1715 cm^{-1}. The ester 4d' was

hydrolyzed to the corresponding dicarboxylic acid by treatment with alcoholic sodium hydroxide and followed with diluted hydrochloric acid. The crude acid was heated with $NaHCO_3$ (ca. 0.5 mol equiv. relative to the carboxylic acid) in refluxing benzene for 1 h. The resulting 4-oxo carboxylic acid was treated with etheral diazomethane to give the methyl ester 5' in 93% yield based on 4d' after column chromatography on silica gel. Desililation of 5' to 6-oxo-$PGF_{1\alpha}$ 11,15-ditetrahydropyranyl ether, which was converted to 6-oxo-PGE_1 (7) by oxidation followed by deprotection,[5] was achieved by treatment with tetrabutylammonium fluoride in THF in 90% yield.

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3) Ref. 2 :This is a just de novo synthesis of 6-oxo-PGE_1, for it has been reported[4,5] on the conversion of $PGF_{2\alpha}$ derivatives to 6-oxo-$PGF_{1\alpha}$ and 6-oxo-PGE_1.

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8) We could not obtain satisfactory results by reductive desulfurization of 4b (Raney nickel, Al(Hg), or PhSNa) and by acid catalyzed hydrolysis of 4c.

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