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SYNTHESIS OF PROSTACYCLIN ANALOGUE (4-OXO-PGI_2)

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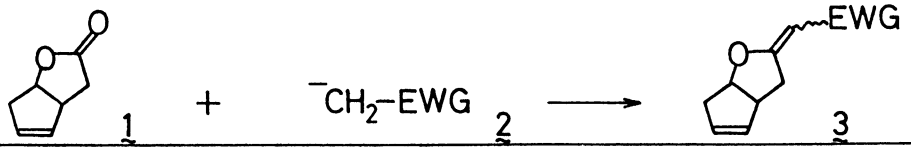
A stable prostaglandin I_2 (PGI_2) analogue, 4-oxo-PGI_2 was synthesized by employing Wittig-like olefin synthesis due to the reaction of a carbanion linked to an electron withdrowing group with a lactone carbonyl group.

Recently, Chinoin group (Galambos et al.) reported[1] the synthesis of 4-oxo-PGI_2. We also describe here a new approach for the synthesis of 4-oxo-PGI_2. Our synthetic strategy is to build the exo-enol ether functionality of prostacyclin by Wittig-like C=C bond formation at the carbonyl of the lactone **4**.

We found out that the carbanion **2** linked to an electron withdrowing group was reacted with γ-butyrolactone **1** to give the exo-enol ether **3** (see Table 1) by procedure as described as follows. Carbanion **2** (2 equiv.) was treated with **1** (1 equiv.) at 0 °C (**2b-e**) or at -78 °C (**2a**) for 30-50 min in THF. The reaction mixture was poured into diluted hydrochloric acid and extracted with ether. The extract was dried well over $MgSO_4$ and concentrated to give **3a-d**.[2] **3e** was obtained after heating of the residue at 105 °C for 1 h. Furthermore, we found out that the products having an active methylene group (**3b**, **3c**, and **3d**) were easily alkylated by usual treatment with alkyl halide and base. This finding prompted us to apply these procedure for the synthesis of 4-oxo-PGI_2.



1 + $^{-}CH_2$-EWG **2** ⟶ **3**

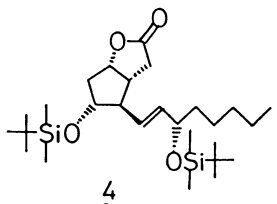
Table 1.

Carbanion (**2**)	Product (**3**)	Yield(%)	(E/Z)[a]
$LiCH_2COOBu^t$ **2a**	EWG=$COOBu^t$ **3a**	86	(9/1-10/1)
$LiCH_2C(ONa)=CHCOOR$	$COCH_2COOR$		
R=Me **2b**	R=Me **3b**	98	(4/1-5/1)
R=Bu^t **2c**	R=Bu^t **3c**	97	(7/1-10/1)
$LiCH_2C(OLi)=CHS(O)Ph$ **2d**	$COCH_2S(O)Ph$ **3d**	89	(4/1-5/1)
PhSCHLiCOOLi **2e**	SPh **3e**	81	(1.5/1)

a) After isolation by column chromatography on silica gel.

Our synthesis of 4-oxo-PGI_2 was carried out as follows. The dianion **2b** derived from methyl acetoacetate (178 mg, 1.54 mmol), NaH (74 mg, ca. 50% of oil suspension, 1.54 mmol), and butyllithium (1.08 ml, 1.56 mol dm^{-3} in hexane, 1.69 mmol), was

treated with lactone 4 (320 mg, 0.64 mmol) in THF at 0 °C for 0.5 h. The reaction mixture was poured into diluted cold hydrochloric acid and extracted with ether. The extract was washed with brine, dried well over $MgSO_4$, and concentrated in vacuo to give 5 (E and Z mixture). The isomers were separated by column chromatography on silica gel to give 5(E) (Rf=0.62, ether/hexane(1/1); 246 mg, 64%) and 5(Z) (Rf=0.29; 72 mg, 19%).[3] Alkylation of 5(E) (145 mg, 0.24 mmol) was carried out by the treatment of 5(E) with ethyl bromoacetate (49 mg, 0.29 mmol) and potassium carbonate (67 mg, 0.49 mmol) in refluxing THF for 12 h to give 6(E) (Rf=0.48, EtOAc/hexane (1/4); 151 mg, 91%).[4] The diester 6(E) (126 mg, 0.185 mmol) was converted to an E and Z mixture of 7 along with non-decarboxylated diester[5] by aqueous alkaline (1 ml, 0.5 mol dm^{-3} NaOH) hydrolysis in dioxane at room temperature, followed by usual workup (acidification, extraction, concentration, and esterification by CH_2N_2). 7(E) (Rf=0.55, EtOAc/hexane(1/4); 55 mg, 49%) and 7(Z) (Rf=0.30; 7 mg, 6%) were separated by column chromatography on silica gel. Deprotection of 7(E) (50 mg, 0.082 mmol) by HF was carried out in aqueous acetonitrile at room temperature for 3 h. The reaction mixture was neutralized (aq $NaHCO_3$), extracted, and worked up usually to yield methyl 4-oxo-PGI_2 8 (E and Z mixture).[6] 8(E)[7] (Rf=0.58, EtOAc; 20 mg, 64%) and 8(Z)[8] (Rf=0.39; 5 mg, 16%) were isolated by column chromatography on silica gel.



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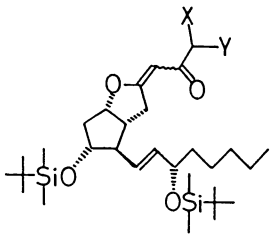
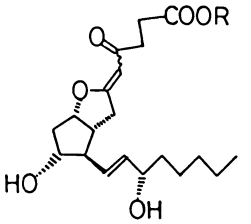


5 X=$COOCH_3$, Y=H
6 X=$COOCH_3$, Y=$CH_2COOC_2H_5$
7 X=H, Y=CH_2COOCH_3



8 R=CH_3, 9 R=H

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References

1) G. Galambos, V. Simonidesz, J. Ivanica, and K. Horváth, Tetrahedron Lett., 24, 1281(1983).
2) It has been reported (B. M. Trost and T. A. Runge, J. Am. Chem. Soc., 103, 7559 (1981)) that an exo-enol ether derivative was obtained by the reaction of 2a with γ-butyrolactone derivative followed by treatment of the product with methanesulfonyl chloride and DBU. However, in our case, the products 3 were obtained directly after usual workup except 3e.
3) ^1H NMR; The active methylene protons and the olefinic proton (exo-enol ether) of 5(E) and 5(Z) were observed at δ 3.41 (s, 2H), 5.77 (br s, 1H) and at δ 3.66 (s, 2H), 5.17 (s, 1H), respectively.
4) 5(Z) was also employed for the synthesis of 8 via 6 and 7 successfully. However, the treatment with acid in the conversions of 6 to 7 and 7 to 8 resulted in a contamination with substantial amounts of E isomers.
5) Methyl ester (ca. 10%) was obtained.
6) Deprotection of 7(Z) gave 8 as an E and Z mixture (E/Z was not constant).
7) 8(E) was converted to an E and Z mixture by treatment of 8(E) with acetic acid in the ratio of 6/1 (E/Z). Hydrolysis of 8(E) by aq KOH in dioxane and diluted hydrochloric acid gave an E and Z mixture of acid 9 (E/Z=4/1, determined by NMR).
8) Hydrolysis of 8(Z) to 9 gave the same result as in the case of 8(E).

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