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AN IMPROVED METHOD FOR THE INTRODUCTION OF CARBON-CARBON TRIPLE BOND AT C-13 IN PG SYNTHESIS

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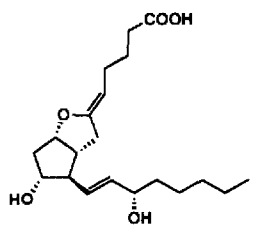
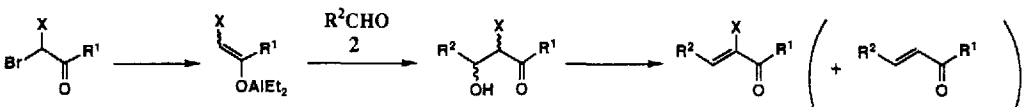
***Abstract** : An improved method for the introduction of carbon-carbon triple bond at C-13 in PG synthesis is described. The efficient aldol reaction of aldehydes has been achieved by using α-chloro enolate anions derived from 1-bromo-1-chloro ketones, giving α-chloro enones after dehydration in good yields, the precursor of the acetylenic alcohols.*



Prostacyclin (1)

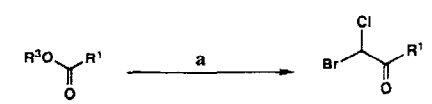
Since the discovery of prostacyclin (PGI_2, **1**) a number of chemically stable PGI_2 analogs have been reported.[1] Furthermore, in order to increase biological activities and metabolical stabilities, many efforts have been focused on the synthesis of PGI_2 analogs. Among these, one of the important structural modifications would be the replacement of a double bond at C-13 (PG numbering) by a triple bond in lower side chain. Therefore, several synthetic methods for 13-dehydro analogs have been reported to date.[2] Previously, we have reported a new method for the introduction of carbon-carbon triple bond at C-13 in PG synthesis through an aldol reaction of the aldehyde (**2**) with α-bromo enolate anion (**5**) generated from the 1,1-dibromo ketone (**3**) and subsequent dehydration as a key step.[3] However, this method was not so satisfactory in regard to yield, because of concomitant formation of the undesired enone (**11**) which was produced through debromination of the α-bromo-β-hydroxy ketone (**7**) with zinc, so that we have continued to study on an improved synthetic method.



In this communication, we wish to report a much improved synthetic method for the introduction of carbon-carbon triple bond at C-13 in PG synthesis.

In order to improve our previous method, we have conducted an aldol reaction of the α-chloro enolate anion (**6**) derived from 1-bromo-1-chloro ketone (**4**), instead of the α-bromo enolate anion (**5**), because the

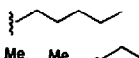
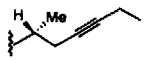
chloro derivative may be preventable from being reduced with zinc. At the outset, the several 1-bromo-1-chloro ketones (**4**) were efficiently synthesized from the esters (**12**) by utilizing (bromochloromethyl)lithium.[4] The results are summarized in Table I.



12 (R^3=Me or Et) **4**

a) BrClCHLi (2.0 equv.), Et_2O-THF (3:2), -100°C ~ -78°C

Table I Synthesis of 1-bromo-1-chloro ketones 4

R^1		yield of 4
	4a	63%
	4b	88%
	4c	72%
	4d	66%

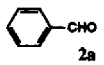
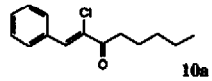
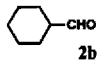
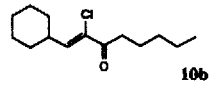
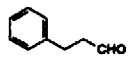
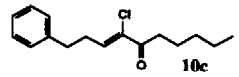
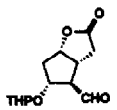
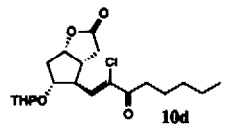
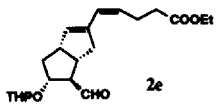
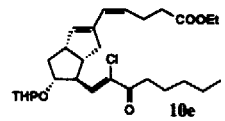
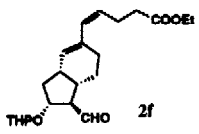
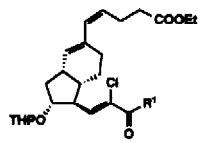
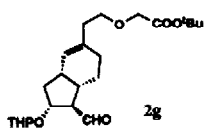
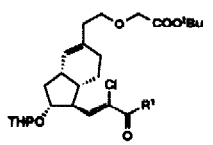
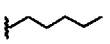
The Corey lactone aldehyde (**2d**) which is a versatile precursor for the synthesis of PG analogs was utilized on a study for the coupling reaction. Treament of the 1-bromo-1-chloro ketone (**4a**) with the aldehyde (**2d**) in the presence of zinc powder and diethylaluminum chloride containing a catalytic amount of copper(I) bromide in THF at -10°C for *ca.* 30 min [3] led to the aldol adduct as a diastereomixture, which was directly converted to the α-chloro enone (**10d**) *via* the mesylate (CH_3SO_2Cl, Et_3N, DBU in CH_2Cl_2) in 84% overall yield (entry 4 in Table II). In this case, the undesired enone was not detected.[5] We presumed that the stereochemistry of **10d** would be a desired *Z* form , which was confirmed by transforming into an authentic material.[6] In the same way, the aldol reaction utilizing various 1-bromo-1-chloro ketones (**4a** - **4d**) was also applicapable successfully to the other aldehyde intermadiates (**2e**, **2f**, **2g**) in PG synthesis as well as some simple aldehydes (**2a**, **2b**, **2c**). Thus, it was shown that the aldol reaction by using the α-chloro enolate anion might be an alternative method to produce a satisfactory result.

Meanwhile, in the course of our synthetic studies for stable PGI_2 analogs, we have already reported the synthesis of homoisocarbacyclin analogs.[7] Among various synthesized analogs, TY-11223 (**16**) containing the acetylenic alcohol moiety in the lower side chain was found to be a very interesting compound.[8] Therefore, our present method was applied to the synthesis of **16**. As expected, the desired α-chloro enone (**10j**) was given in excellent yield compared to our previous method by using α-bromo enolate anion (entry 10).

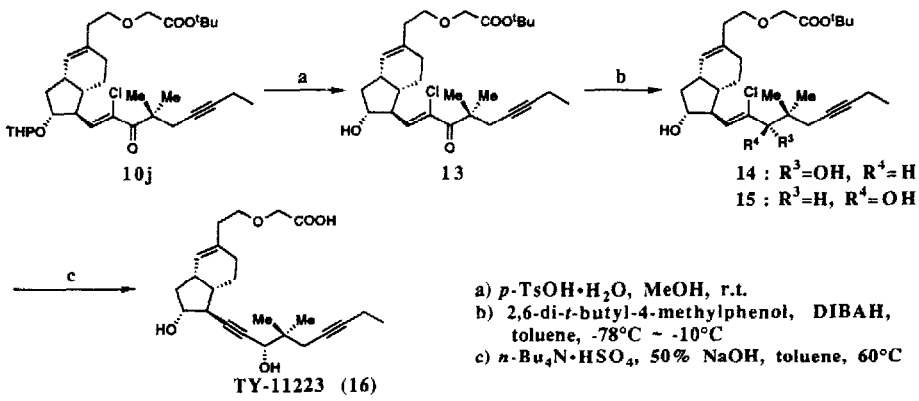
With the precursor of the acetylenic alcohol in hand, we finally attempted a conversion of the α-chloro enone (**10j**) to **16**. Deprotection of **10j** with *p*-toluenesulfonic acid in methanol at r.t. afforded the alcohol (**13**) , which was reduced with diisobutylaluminum-2,6-di-*t*-butyl-4-methylphenoxide to give the diol (**14**) in 79% overall yield together with the undesired diol (**15**) (11%).[9] The diol (**14**) was transformed into **16** in one step (88%) on exposure to 50% aqueous NaOH (toluene, n-$Bu_4N{\bullet}HSO_4$, 60°C, 12 hr), whose spectral data were identical with those of an authentic material.[10]

In conclusion, we have developed a general method for the conversion of aldehydes to α-chloro enones, the precursors of acetylenic alcohols, which has made it possible to achieve a much improved synthesis of **16**. By the use of this versatile synthetic technology, various 13-dehydro PG analogs and other biologically interesting compounds containing an acetylenic alcohol moiety would be readily available from the corresponding aldehydes.

Table II Preparation of α-chloro enones (10)

entry	aldehydes 2	4 (or 3)	yield of α-chloro enones 10 [a] (yield of 9 [b])
1	 2a	4a	 10a y. 93%
2	 2b	4a	 10b y. 93%
3	 2c	4a	 10c y. 87%
4	 2d	4a	 10d y. 84% (42%)
5	 2e	4a	 10e y. 84% [c]
	 2f		
6	2f	4a	10f : R^1=  y. 84% (60%)
7	2f	4b	10g : R^1=  y. 82% (53%)
8	2f	4d	10h : R^1=  y. 92% (54%)
	 2g		
9	2g	4a	10i : R^1=  y. 90% (59%)
10	2g	4b	10j : R^1=  y. 85% (42%)
11	2g	4c	10k : R^1=  y. 76% (63%)
12	2g	4d	10l : R^1=  y. 89% (60%)

a) All aldol reactions were carried out at -20°C to 0°C.
b) In every case the undesired enones were produced in 10 - 14% yield.
c) The spectral data of 10e showed to be Z form in comparing to the reported data. : see ref. 2c).



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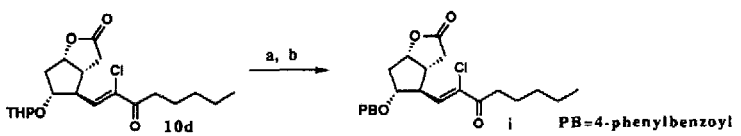
5. In the aldol reaction of **2d** with α-bromo enolate anion, the enone (**11d**) was chromatographycally separated to afford in *ca.*10% yield.
6. C. Gandolfi, G. Doria and P. Gaio., *Il Farmaco, Ed. Sc.*, **1972**, *27*, 1125.
   10d was transformed into **i** by shown below. The NMR spectrum of **i** in $CDCl_3$ solvent showed a vinylic proton at C-13 (PG numbering) δ 6.80 (d, J=9.0Hz). : lit. δ 6.78 (d, J=9.1Hz), m.p. 150 - 151°C : lit. 151 - 152°C.



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   b) A. Takahashi and M. Shibasaki, *Tetrahedron Lett.*, **1987**, *28*. 1893.
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10. The spectral data of **16**. $[\alpha]_D^{27}$ = + 61.58° (c=1.01, CH_3OH), ^{1}H-NMR ($CDCl_3$)δ: 1.04 (s, 3H), 1.08 (s, 3H), 1.12 (t, J=7.2Hz, 2H), 4.04 (s, 2H), 4.10 (m, 3H), 4.26 (d, J=2.0Hz, 1H), 5.38 (bs, 1H), IR (neat)ν_{max}: 3406, 2968, 2920, 2230, 1734, 1434, 1320 cm^{-1}, MS m/z : 403 $(M+H)^+$.

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