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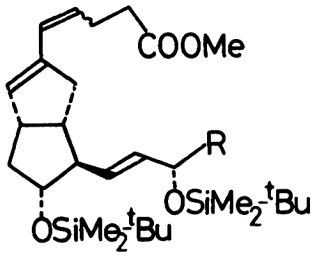
SYNTHESIS OF (Z)-4,5,13,14-TETRADEHYDRO-9(O)-METHANO-$\Delta^{6(9\alpha)}$-PGI_1

Katsuhiko ISEKI,* Masaki SHINODA, Chiyoko ISHIYAMA, Yosio HAYASI,
Shun-ichi YAMADA,† and Masakatsu SHIBASAKI††
Research Laboratory, Mitsubishi Yuka Pharmaceutical Co., LTD.,
Ami, Inashiki, Ibaraki 300-03
†Faculty of Pharmaceutical Science, Josai University,
Keyakidai, Sakado, Saitama 350-02
††Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229

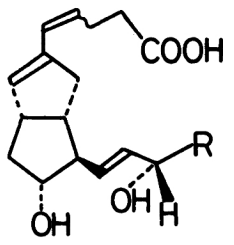
A stereoselective synthesis of (Z)-4,5,13,14,-tetradehydro-9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1, a potent prostacyclin analog, has been accomplished.

The conjugated dienes (**1-4**) were demonstrated to be the key intermediates for some carbacyclins, intravenous and orally active prostacyclin derivatives.[1] The deprotected dienes (**5-8**) were found to be also highly stable and biologically potent analogs which might be of therapeutic value for occlusive peripheral vascular diseases, etc. The 4-Z stereoisomer of **7** is approximately one hundred times as potent as the 4-E isomer in inhibiting human platelet aggregation and the separation of the stereoisomer **7** is extremely difficult.[2] In this communication we wish to report a solution to this serious synthetic problem and the synthesis of a new prostacyclin analog **9** which contains the triple bond at C_{13}-C_{14} (PG numbering).[3]

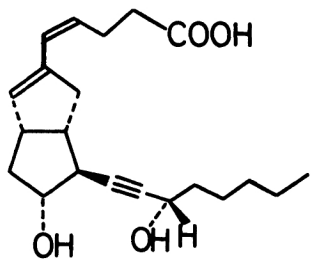
Wittig reaction of the α,β-unsaturated aldehyde **10** with the ylide derived from 3-carboxypropyltriphenylphosphonium bromide (**13**) and potassium t-butoxide in THF gave the mixture of the stereoisomers **11** (E:Z = ca. 1:2).[4] We have examined



1 R = n-C_5H_{11}
2 R = cyclopentyl
3 R = $CH(CH_3)CH_2C{\equiv}CCH_3$
4 R = $CH_2CH(CH_3)CH_2CH_2CH{=}C(CH_3)_2$



5 R = n-C_5H_{11}
6 R = cyclopentyl
7 R = $CH(CH_3)CH_2C{\equiv}CCH_3$
8 R = $CH_2CH(CH_3)CH_2CH_2CH{=}C(CH_3)_2$



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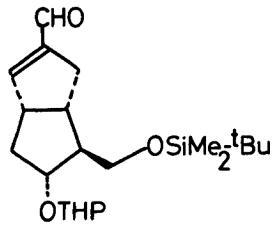
the reaction of **10** with the ylides derived from the phosphonium bromides (**14** and **15**)[5] under a variety of conditions. Table 1 summarizes the representative results. The Z/E ratio was determined by 270-MHz NMR spectra.[6] We found that treatment of **10** with the ylide derived from **15** and potassium t-butoxide in THF at -78 °C for 1.5 h afforded the conjugated diene **12** in 93% yield and, very fortunately, in an extremely high stereoselectivity (Table 1, entry 5).



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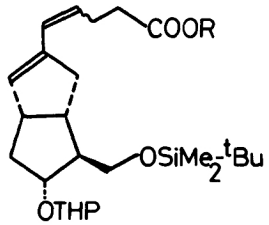


11 R = H
12 R = Et

Br^-
$Ph_3P^+CH_2CH_2CH_2COOR$

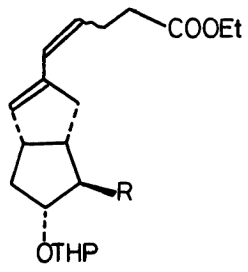
13 R = H
14 R = Me
15 R = Et

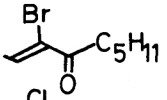
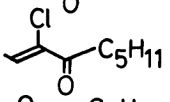
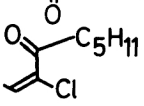
Table 1. Wittig reaction of **10** with the ylides derived from **14** and **15**

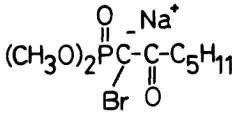
Entry	Phosphonium bromide	Base	Solvent	Temp/ °C	Z : E	yield / %[a]
1[b]	**13**	t-BuOK	THF	r.t.	1 : 2	85
2[c]	**14**	t-BuOK	THF	r.t.	-	-
3	**15**	dimsyl Na	DMSO	r.t.	89 : 11	96
4	**15**	t-BuOK	THF	r.t.	87 : 13	94
5[d]	**15**	t-BuOK	THF	-78	>98 : <2	93
6[d]	**15**	NaH	DMF	-60	94 : 6	81

a) All yields are for isolated pure compounds. b) See Ref. 4. c) The substrate **10** was recovered. d) The reaction mixture was gradually warmed to room temperature over 2 h to be quenched with aqueous NH_4Cl solution.

With the high stereoselectivity described above, we next turned our attention to the conversion of the key intermediate **12** to the α-bromoenone **18** which would be transformed to the new prostacyclin analog **9**. Treatment of **12** with $Bu_4N^+F^-$ in THF gave the alcohol **16** in quantitative yield. Oxidation of **16** with SO_3-pyridine complex and triethylamine in DMSO gave the aldehyde **17**, which was directly treated with the anion **21** derived from dimethyl (2-oxoheptyl)phosphonate, N-bromosuccinimide, and sodium hydride in situ according to the method reported by Vorbrüggen and co-workers.[7] However, the desired product **18** was not obtained.



16 R = CH_2OH
17 R = CHO
18 R = 
19 R = 
20 R = 



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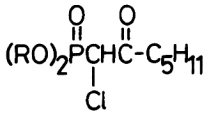


22 R = Me
23 R = i-Pr

Table 2. Reaction of the aldehyde **17** with the phosphonates (**22** and **23**)

Entry	Phosphonate	Base	Solvent	Yield / %[a]	
				19	**20**
1	**22**	NaH	DME	31	49
2	**23**	NaH	DME	57	21

a) All yields are for isolated pure compounds.

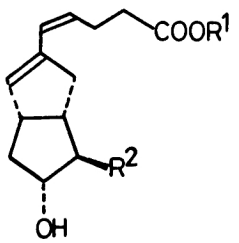
b) The molar ratio of **17**/**22** (or **23**)/NaH is 1.0 : 2.0 : 1.5.

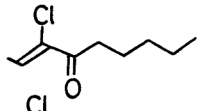
Therefore, the α-chlorophosphonate (**22** and **23**)[8] has been examined (Table 2). Reaction of **17** with **22** and sodium hydride in 1,2-dimethoxyethane at room temperature for 24 h gave the Z-enone **19**[9] in 31% yield together with the E-enone **20**[10] (49%)(Table 2, entry 1). Instead of **22**, use of **23** under the same conditions gave **19** in 57% yield together with **20** (21%)(Table 2, entry 2).

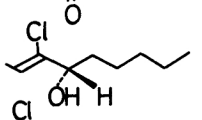
The Z-enone **19** was then transformed to the new carbacyclin analog **9** in the following manner. Deprotection of **19** with 65% aqueous acetic acid at 50 °C for 2 h afforded the alcohol **24**, which was reduced with diisobutylaluminum-2,6-di-t-butyl-4-methylphenoxide[11] to give the more polar diol **25** in 56% overall yield together with the less polar diol **26** (22%). Elimination of **25** with potassium t-butoxide in THF at room temperature for 3 h followed by treatment with ethereal diazomethane gave the diol **27** in 67% yield. Finally, hydrolysis of **27** with sodium hydroxide in aqueous ethanol followed by acidic extraction provided (Z)-4,5,13,14-tetradehydro-9(0)-methano-$\Delta^{6(9\alpha)}$-PGI_1 **9**[12] as a colorless oil in 92% yield.

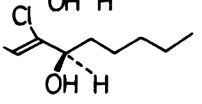
Preliminary biological results obtained with **9** indicated potent inhibitory activity in human platelet aggregation.[13]

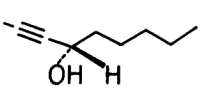
The authors are grateful to Mr. Kanayama and Miss Jindo for test of biological activities.



24 R^1 = Et R^2 = 

25 R^1 = Et R^2 = 

26 R^1 = Et R^2 = 

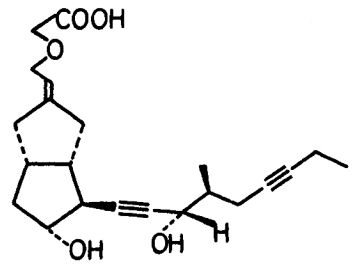
27 R^1 = Me R^2 = 

References

1) M.Shibasaki, M.Sodeoka, and Y.Ogawa, J. Org. Chem., 49, 4096 (1984).

2) The stereoisomers **7** were separated by $AgNO_3$-impregnated silica gel column chromatography, unpublished result by M.Shibasaki, Y.Ogawa, M.Sodeoka, and T. Mase in Sagami Chemical Research Center.

3) ZK-96480 (**28**) containing the triple bond at C_{13}-C_{14} (PG numbering) was described to be metabolically stable and therefore orally active in rats up to 48 h, see: H.Vorbrüggen, W.Skuballa, and B.Radüchel, Kyoto Conference on Prostaglandins, Kyoto, 1984, Abstr., p.36.



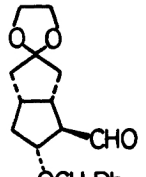
ZK-96480 (28)

4) M.Sodeoka and M.Shibasaki, Chem. Lett., 1984, 579.

5) Reflux of triphenylphosphine and methyl 4-bromobutyrate in acetonitrile gave the phosphonium bromide **14**. Under the same conditions, **15** was prepared from ethyl 4-bromobutyrate.

6) The NMR spectrum of the 4-E isomer (**12**) in $CDCl_3$ solvent showed one proton d (δ 6.24, J=16 Hz) and for the 4-Z isomer (**12**) was shown one proton d (δ 5.98, J=11 Hz).

7) Conversion of the aldehyde **29** to the α-bromoenone **30** was described by H. Vorbrüggen in Kyoto Conference on Prostaglandins (1984), see Ref. 3.



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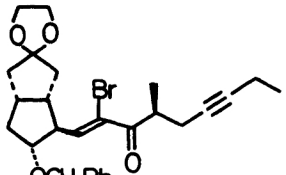

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8) Dialkyl (1-chloro-2-oxoheptyl)phosphonate was easily prepared by treatment of dialkyl (2-oxoheptyl)phosphonate with sodium hydride (2 equiv.) and N-chlorosuccinimide (1 equiv.) in 1,2-dimethoxyethane at room temperature.

9) PMR($CDCl_3$)δ(ppm): 6.85(d, J=10.4 Hz, 1H), 6.00(d, J=11 Hz, 1H), 5.58(s, 1H), 5.35(m, 1H), 4.60(m, 1H), 4.12(q, J=7.1 Hz, 2H), and 1.27(t, J=7.1 Hz, 3H). IRν_{max}(neat): 2930, 1735, 1690, and 1610 cm^{-1}. Mass m/z: 492(M^+),410, 408, 216, 117, and 85.

10) PMR($CDCl_3$)δ(ppm): 6.03(two d, J=11 Hz, 2H), 5.60(s, 1H), 5.35(m, 1H), 4.68(m, 1H), 4.16(q, J=7.1Hz, 2H), and 1.27(t, J=7.1Hz, 3H). IRν_{max}(neat): 2930, 1735, 1693, and 1600 cm^{-1}. Mass m/z: 492(M^+), 449, 447, 410, 408, 216, 117, and 85.

11) S.Iguchi, H.Nakai, M.Hayashi, and H.Yamamoto, J. Org. Chem., 44, 1363 (1979).

12) PMR($CDCl_3$)δ(ppm): 6.01(d, J=11.2 Hz, 1H), 5.60(s, 1H), 5.38(m, 1H), 4.39(m, 1H), 4.03(m, 1H), 3.14(m, 1H), and 0.90-2.95(m, 21H). IRν_{max}(neat): 3350, 2930, 2230, 1705, 1450, 1410, 1265, 1090, and 840 cm^{-1}. Mass m/z: 346(M^+), 328, 310, 237, 117, and 43.

13) The new prostacyclin analog **9** was approximately as potent as PGE_1 in inhibiting human platelet aggregation induced by ADP.

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