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# SYNTHESIS OF (±)-5,6,7-TRINOR-4,8-INTER-m-PHENYLENE PGI $_2$[1)]

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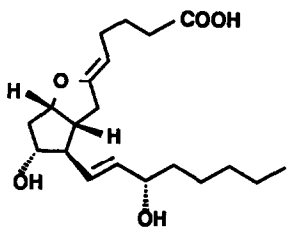
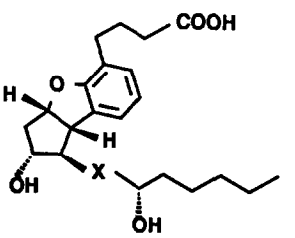
Abstract: A stable and potent analog of prostacyclin, the titled compound, and its derivative were synthesized from readily available 1,4-dibromocyclopentene via 5-(4-tetrahydropyranyloxybutyl)cyclopenta[b]benzofuran **7**.

Prostacyclin ($PGI_2$, **1**) has potent biological activities such as inhibition of platelet aggregation and vasodilation[3)]. The activities of $PGI_2$ are attractive for remedy of some diseases in circulatory system. However, the clinical applications of the compound have been limited to parenteral administration owing to the chemical instability due to a labile enol ether linkage. $PGI_2$ **1** is rapidly hydrolyzed even under neutral condition to give 6-oxo-$PGF_{1\alpha}$ which has little biological activity. Therefore, extensive efforts have been made to synthesize stable and potent analogs[4)]. One reasonable approaches to improve the instability of $PGI_2$ is to replace the enol ether linkage by a substituted phenoxy group. In this communication, we wish to report synthesis of two stable and potent analogs, the titled compound **2** (X=trans CH=CH) and its acetylenic derivative **3** (X= C-C).




$PGI_2$ **1**



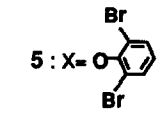

*m*-Phenylene$PGI_2$
**2** : X= CH=CH
**3** : X= C≡C

Substitution of readily available cis-1,4-dibromocyclopent-2-ene **4**[5)] with potassium 2,6-dibromophenoxide in the presence of 2.0 molar% of 18-crown-6 in DME afforded cis-1,4-bis(2,6-dibromophenoxy)cyclopent-2-ene **5** (75%). Metalation of the bromide **5** with 1.5 equivalents of n-butyllithium at -78 °C in anhydrous THF followed by cyclization at -10 °C gave 5-bromo-3H-cyclopenta[b]benzofuran **6** (46%). Lithiation of the resulting bromide **6** with 1.0 equivalents of n-butyllithium at -78 °C and subsequent alkylation with 4-iodobutyl tetrahydropyranyl ether gave a key intermediate, 5-(4-tetrahydropyranyloxybutyl)cyclopenta[b]benzofuran derivative **7** (86%).

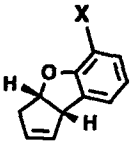
Stereoselective hydroxybromination of the cyclopenta[b]benzofuran **7** with NBS in DMSO-water-THF at 0 °C followed by cyclization with $K_2CO_3$ in methanol afforded syn-epoxide **8** (45% overall from **7**). In the hydroxybromination, desired bromohydrin **8a** was obtained as a major product (50%) along with small amounts of undesired **8b** and **8c**. The stereoselectivity (**8a**:**8b**+**8c** = ca.5:1) is considered to be due to a predominant attack of a bromonium cation from less hindered β-side of **7**[6)]. Addition of 1,3-bis(methylthio)-

propenyllithium[7] to the epoxide **8** gave a mixture of **9a** and **9b** (1:1)[8], which were separated by column chromatography (silica gel) to afford pure compound **9a**. The resultant thioenol ether **9a** was hydrolyzed with $HgCl_2$-$CaCO_3$[7] afforded enal derivative **10a** (51%).

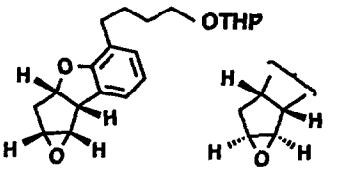
**4** : X= Br



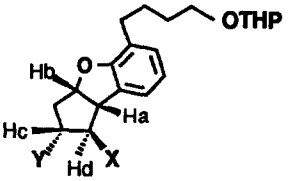
**5** : X= O



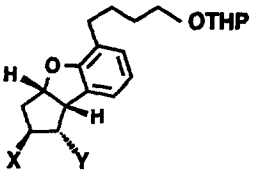
**6** : X= Br
**7** : X= $(CH_2)_4OTHP$



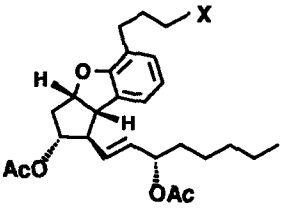
**8** **8'**



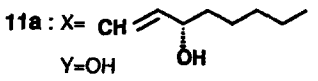
**8a** : X= Br, Y= OH
**8b** : X= OH, Y= Br
**9a** : X= CH(SMe)CH═CHSMe
Y= OH
**10a** : X= CH═CHCHO
Y= OH



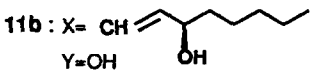
**8c** : X= OH, Y= Br
**9b** : X= CH(SMe)CH═CHSMe
Y=OH
**10b** : X = CH═CHCHO
Y = OH



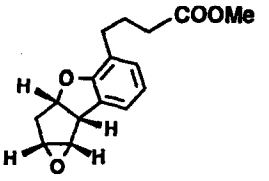
**12** : X= $CH_2OTHP$
**13** : X= $CH_2OH$
**14** : X= COOH



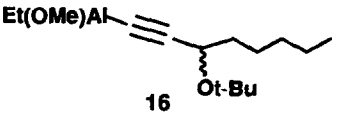
**11a** : X= CH
Y=OH



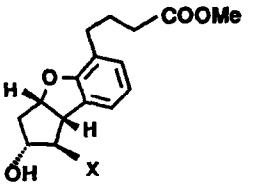
**11b** : X= CH
Y=OH

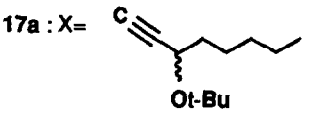


**15**

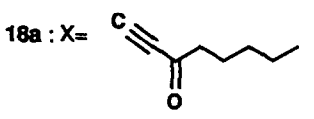


**16**

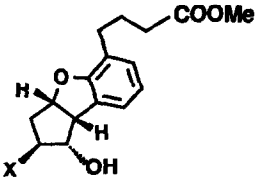


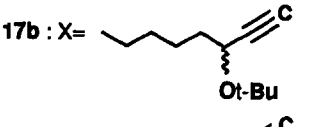


**17a** : X=

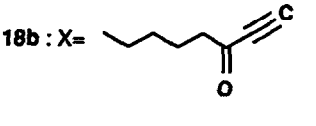


**18a** : X=





**17b** : X=



**18b** : X=

The titled compound **2** (X=trans CH=CH) was synthesized from the aldehyde **10a** by the following sequences: (a) addition of n-pentyl lithium in anhydrous THF and separation of stereoisomers (**11a**: 45% and **11b**: 30%)[9], (b) Acetylation of **11a** with $Ac_2O$ in pyridine (**12**: 93%), (c) hydrolysis of THP ether with 0.1N HCl in MeCN/THF (**13**: 74%), (d) oxidation with pyridinium dichromate in anhydrous DMF[10] (**14**: 88%), and (e) deacetylation with 1N NaOH (**2**: 97%)[11].

An intermediate for synthesis of the acetylenic compound **3** (X= C-C), epoxy ester **15**, was synthesized from the key intermediate **7** as follows: (a) hydrolysis of THP ether with HCl (61%), (b) oxidation with pyridinium dichromate and methylation with diazomethane (46%), and (c) treatments with NBS/DMSO-water and then $K_2CO_3$ (62%)

For an elongation of $\omega$-side chain, 3-t-butoxy-1-propyne was prepared by coupling reaction of hexanal and magnesium acetylide[12] followed by protection hydroxyl group with isobutylene[13]. Metalation of the acetylene of 3-t-butoxy-1-propyne with n-butyllithium in toluene at 0 °C and then with ethyl methoxy aluminum chloride at 0 °C led to aluminum acetylide **16**[14], which was coupled with the epoxide **15** at an ambient temperature to give alcohol **17a** and its regioisomer **17b** (32% and 28%, respectively)[15]. The alcohol **17a** was deprotected with trifluoroacetic acid[13] and then with 1N NaOH to afford the acetylenic derivative **3** (X= C-C; 40% from **17a**)[16]. In the case of the acetylenic derivative, stereoisomers of the hydroxyl group in $\omega$-side chain were not separable on chromatography[17][18].

The compounds exhibited potent inhibitory effects on human platelet aggregation induced by ADP[19].

## References and Notes


1) Part IX of the synthesis of prostaglandins and their analogs. For part VIII, K.Ohno, H.Nagase, K.Matsumoto, H.Nisiyama and S.Nishio, "Advances in Prostaglandin, Thromboxane, and Leukotriene Research", Vol.15, p.279, Raven Press, **1985**.

2) Present address: School of Material Science, Toyohashi University of Technology, Tenpaku-cho, Toyohashi, Aichi, 440 Japan

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4) a) W.Skuballa, E.Schillinger, C.-St.Sturzebecher and H.Vorbruggen, J. Med. Chem., **1986**, 29, 313. b) W.Bartmann and G.Beck, Angew. Chem. Int. Ed. Engl., **1982**, 21, 751 and references sited therein.

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6) The stereochemistry of **8a**, **8b**, and **8c** was determined as follows; after conversion of these bromohydrins to the epoxides (**8a** to syn-epoxide **8**, and **8b** and **8c** to anti-epoxide **8'**), the stereochemistries of each epoxides were determined by $^1$H-NMR spectra (normal and decoupling).

7) E.J.Corey, B.W.Erickson and R.Noyori, J. Am. Chem. Soc., **1971**, 93, 1724.

8) The structure of **9a** and **9b** were determined as follows; after conversion of the thienol ethers **9a** and **9b** to corresponding enal derivertives **10a** and **10b**,the structures of these enals were determined by $^1$H-NMR and

decoupling (for example, on irradiation of proton b of the compound **10a**, the protons a and d were decoupled, on the other hand, the irradiation of proton d gave decoupling of protons a and c).

9) We temporarily regarded the more polar compound, **11a** on TLC (Rf: **11a** = 0.39, **11b** = 0.47 silica gel plate; cyclohexane:EtOAc = 1:3) as 15$\alpha$ hydroxy one and the less polar one, **11b** as 15$\beta$ one. Further, after conversion of each compounds to corresponding diol acids 1 and 1', the biological activities of each acids were compared (the more polar one 1 derived from **11a** showed more potent activity than the less polar one 1' derived from **11b** on the inhibition of human platelet aggregation induced by ADP. The X-ray analysis of the compound 1 to determine the stereochemistry of 15-hydroxy group are examining and will be published in Tetrahedron near future.

10) E.J.Corey and G.Schmidt, Tetrahedron Lett., **1979**, 399.

11) Spectoral data of the titled compound **2**. IR(liquid film): 3600-2500, 2920, 2850, 1710, 1590, 1440, 1250, 1180, 1020, 965, 860, 740cm$^{-1}$. $^1$H-NMR (100MHz, $CDCl_3$)$\delta$: 0.90(3H,t,J=7Hz), 1.2-1.6(18H,m), 1.8-2.1(3H,m), 2.35 (2H,m), 2.5(2H,m), 2.63(2H,m), 3.40(1H,t,J=8Hz), 3.9(1H,m), 4.1(1H,m), 4.8(3H,broad), 5.1(1H,m), 5.6(2H,m), 5.6(2H,m), 6.7-7.0(3H,m). MS(m/e): 388($M^+$), 370, 352, 218.

12) a) L.Brandsma, "Preparative Acetylenic Chemistry", p.71, Elsevier, **1971**. b) N.Rabjohn, "Organic Synthesis", Coll. Vol.4, p.792, John Wiley, **1963**.

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14) a) J.Fried and J.C.Sih, Tetrahedron Lett., **1973**, 3899. b) J.Fried, D.K.Mitra, M.Nagarajan and M.M.Mehrotra, J. Med. Chem., **1980**, 23, 234.

15) The structure of **17a** and **17b** were determined by $^1$H-NMR and decoupling in a similar manner as in the case of **9a** and **9b** after conversion of **17a** and **17b**to $\alpha,\beta$-unsaturated ynone **18a** and **18b**, respectively.

16) Spectral data of the acetylenic derivative **3**. IR(liquid film): 3600-2500, 2930, 2850, 2230, 1710, 1595, 1450, 1250, 1190, 1030, 865, 745 cm$^{-1}$. $^1$H-NMR (90MHz, $CDCl_3$)$\delta$: 0.90(3H,t,J=6Hz), 1.2-1.8(8H,m), 2.2-2.6(4H,m), 2.31(2H,t,J=7Hz), 2.62(2H,t,J=7Hz), 2.80(1H,td,J=6 and 2Hz), 3.77(1H,dd, J=8 and 2Hz), 4.11(1H,q,J=6Hz), 4.40(1H,td,J=6 and 2Hz), 5.10(4H,broad), 6.78(1H,t,J=7Hz), 6.97(1H,dd,J=7 and 1Hz), 7.12(1H,dd,J=7 and 1Hz). MS(m/e): 386($M^+$), 368, 218. High resolution MS: Obsvd. 386.2095. Calcd. 386.2093 as $C_{23}H_{30}O_5$.

17) We are synthesizing of the analog as an optical active form and will publish the result in Tetrahedron.

18) The $^1$HNMR spectrum did not showed any peak regarded as the mixture of stereoisomers of 15-hydroxy group.

19) The authors thank Dr. Shintaro Nishio at BRL for pharmacological assays of the synthesized compounds.

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