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SYNTHESIS OF 9(O)-METHANO-$\Delta^{6(9\alpha)}$-PGI_1: THE HIGHLY POTENT CARBON ANALOG OF PROSTACYCLIN

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Summary: A new Prostacyclin analog, 9(O)-Methano-$\Delta^{6(9\alpha)}$-PGI_1, was synthesized by utilizing intramolecular pinacolic coupling reaction as the key step and was shown to be more potent than carbacyclin in inhibition of platelet aggregation.

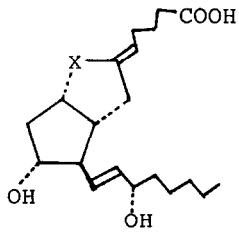
Since prostacyclin (PGI_2) 1 was found to be the most potent inhibitor of human platelet aggregation and also a powerful vasodilator with fairly short half-life, considerable efforts have been devoted to prepare chemically more stable and biologically more selective analogs.[1]

We[2] and other groups[1] have independently reported the synthesis of 9(O)-methanoprostacyclin (carbacyclin) 2, which is one of the most promising analog.[3] With the aim of developing more attractive compounds we successively synthesized the carbon analog 3[4] of Δ^6-PGI_1 and the sulfur analog 4.[5] In contrast to the interesting biological profile of 5,[6] these stable analogs were found to be much less active than PGI_2 1. On the other hand, a synthesis of 9-deoxy-9α,6-nitrilo-PGI_1 6 has been described by Bundy and Baldwin[7] and interestingly, 6 was found to be equipotent to PGI_2 as an inhibitor of platelet aggregation. These results prompted us to prepare the new carbon analog 7, which contains the double bond at C_6-$C_{9\alpha}$ (PG numbering). We report herein the first synthesis of 7 and its potent preliminary biological activities (Scheme-I).

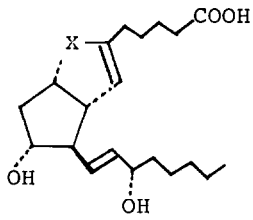
As the heart of the present synthesis lies the regiospecific construction of the bicyclo-[3.3.0]oct-2-ene skeleton. Toward this end, model studies were carefully carried out, indicating that the keto-aldehyde 8[8] was a reasonable synthetic intermediate for the present purpose. Thus, intramolecular pinacolic coupling reaction of 8 by the use of $TiCl_4$-Zn in THF at 0°C[9] afforded the bicyclic diol 9[8,10] as a major product, which was efficiently converted to the desired endo-olefin 11[8] via the α-epoxide 10[10] (Scheme-II).

Applying this methodology, the requisite prostanoid keto-aldehyde 17 was prepared from the readily available and optically active ketone 12 as illustrated in Scheme-III. Methylenation of 12[11,12] was effectively carried out by the action of Zn-CH_2Br_2-$TiCl_4$[13] to afford 13[8] in 80% reproducible yield. Careful hydroboration of 13 with 9-BBN in THF at 0°C followed by treatment with alkaline hydrogen peroxide[12] led to the corresponding primary alcohol 14[8] (64.5%). Iodoetherification[14] of 14 and subsequent treatment with DBU in toluene at 50-60°C gave the enol ether 15 as a major product, which was directly converted to the keto-alcohol 16[8] in AcOH-H_2O-THF (1:1:1) at room temperature (56.7% from 14). Oxidation of 16 was best carried out by

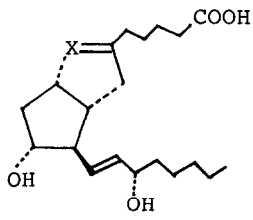
Scheme-I



1: X=O
2: X=CH_2

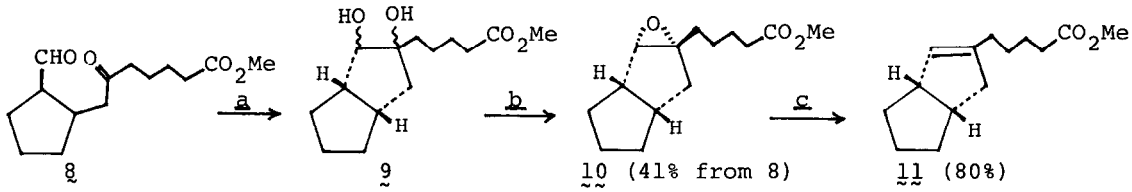


3: X=CH_2
4: X=S
5: X=O



6: X=N
7: X=CH

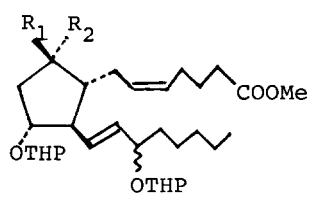
Scheme-II



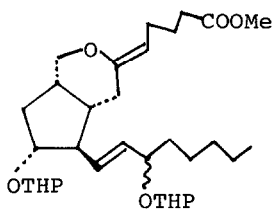
8 → 9 → 10 (41% from 8) → 11 (80%)

a, $TiCl_4$,Zn,THF,0°C,3 hr. b, i)MsCl,Et_3N,CH_2Cl_2,-25°C; ii)DBU,toluene.
c, i)NaI-$(CF_3CO)_2O$,THF,room temp.; ii)Zn,room temp.⟶60°C.

Scheme-III



12: R_1-R_2=O
13: R_1-R_2=CH_2
14: R_1=H, R_2=CH_2OH



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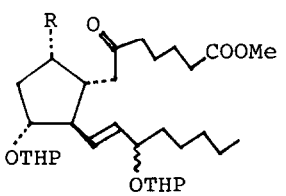
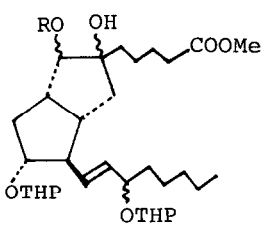
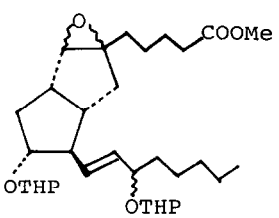


16: R=CH_2OH
17: R=CHO



18: R=H
19: R=Ms



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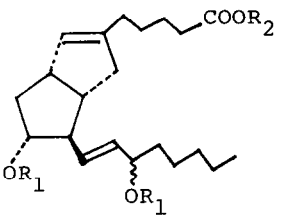

21: R_1=THP, R_2=Me
22: R_1=H, R_2=Me (15β-OH)
23: R_1=H, R_2=Me (15α-OH)
24: R_1=R_2=H (15β-OH)

the action of excess SO_3·pyridine complex[15] to furnish the requisite keto-aldehyde 17. Owing to its instability, 17 was immediately treated with $TiCl_4$-Zn in THF at 0°C to afford the bicyclic diols 18 as a diastereomeric mixture. Crude 18 was carefully mesylated (1.5 molar equiv MsCl-Et_3N, CH_2Cl_2, -25°C) to afford the crude mesylate 19, which was directly treated with DBU at room temperature to furnish the epoxide 20[8,16] in 25% yield from 16. Reaction of 20 with NaI-$(CF_3CO)_2O$ in THF at room temperature followed by the addition of excess zinc powder[17] gave the desired endo-olefin 21[8] in 44% yield along with recovered 20 (~40%). Treatment of 21 with AcOH-H_2O-THF (3:1:1) at 50°C for 1 hr caused a clean deprotection to afford an easily separable C_{15} alcohol mixture of the diols in 75% yield. The less polar isomer (Rf 0.31, ether) could be assigned as the 15β-isomer 22,[8] while the more polar isomer (Rf 0.13) as the 15α-isomer 23[8] on the basis of their biological profile and independent synthesis.[18] Finally, hydrolysis of 23 with 5M-NaOH in THF-H_2O (3:1) at 40°C followed by acidic extraction furnished the new prostacyclin analog 7[19] quantitatively (Scheme-III).

Preliminary biological results indicate that the potency of 9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1 7 is one-tenth as active as that of prostacyclin 1 in inhibiting platelet aggregation induced by ADP in rabbit platelet rich plasma,[20] while the 15β-isomer 24 was about five-hundredths as active. Furthermore, this stable analog 7 showed the nearly equipotent cytoprotective action[21] to PGE_2 (rabbit stomach epithelial cells). These results are extremely instructive for developing a new drug as well as understanding structure-activity relationships of the carbon analogs of prostacyclin 1.

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References and Notes

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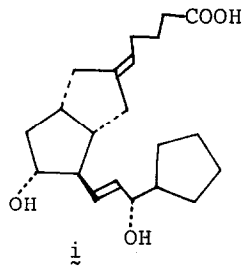

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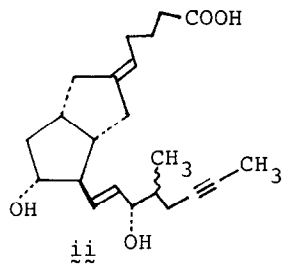

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16) Stereochemistry of the epoxy moiety of 20 is not clear at present.

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18) M.Shibasaki, H.Fukasawa, and S.Ikegami, consecutive paper in this issue.

19) IR ν_{max}(neat) cm^{-1}: 3350, 2910, 2850, 1700, 1450, 1250. PMR($CDCl_3$) δ(ppm): 5.55 (m, 2H), 5.30 (bs, 1H), 4.55 (m, 3H), 4.10 (m, 1H), 3.75 (m, 1H), 3.00 (m, 1H), 2.75 2.20 (m, 4H), 2.20 1.90 (m, 2H). MS (CI, NH_3) m/e: 368 ($M^+ + NH_4$). mp. 73 79°C. $[\alpha]_D^{25}$+16.0° (c 0.25, MeOH).

20) IC_{50}(g/ml): 7; 34 x 10^{-9}, PGI_2; 3~5 x 10^{-9}, 24; 1.9 x 10^{-6}. Inhibitory activity of 7 using human PRP was found to be about half of that of PGI_2.

21) For detail of the assay, see K.Matsuoka, Y.Mitsui, and S.Murota, J. Pharm. Dyn., 5, 911 (1982).

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