SYNTHESIS OF A NEW CHEMICALLY STABLE PROSTACYCLIN ANALOGUE WITH HIGH AND LONG-LASTING ACTIVITY

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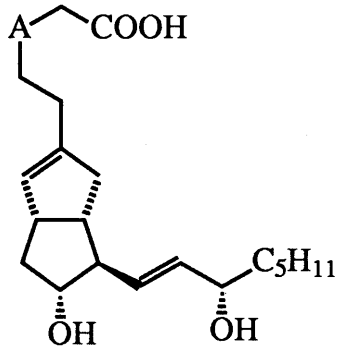
The chemically stable prostacyclin analogue *(Z)*-4,5-didehydroisocarbacyclin analogue (**6**) has been synthesized. Compound **6** given intravenously or orally is very potent in inhibiting platelet aggregation.

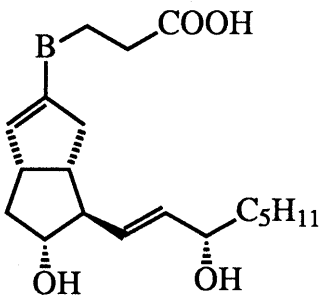
KEYWORDS prostacyclin; isocarbacyclin; platelet aggregation; hypotensive effect

The biological potency of natural prostacyclin (PGI_2) coupled with its inherent instability has resulted in a large number of synthetic analogues in a search for chemically stable and therapeutically useful mimics. Carbacyclin is a well-known and biologically potent carbon analogue in which the oxygen atom at the C-9 position is replaced by a methylene group.[2)] In 1983, Ikegami and his colleagues reported a new carbon analogue isocarbacyclin (**1**) which is more potent than carbacyclin in inhibiting platelet aggregation.[3)] Kojima's group successfully replaced the methylene group in the 3-position of isocarbacyclin by an oxygen atom to prevent the ß-oxidation of the upper side chain (**2**).[4)] Here we report a chemically stable *(Z)*-4,5-didehydroisocarbacyclin analogue KP-10614 (**6**) with high oral activity.[5)] We have examined the biological activities of isocarbacyclin analogues in which the ethylene group at C_4-C_5 was replaced by an unsaturated bond. Although compound **3**[6)] and **4** show only very weak inhibitory activities in human platelet aggregation induced by ADP, *(Z)*-4,5-didehydroisocarbacyclin (**5**) is more potent than isocarbacyclin (**1**) (Table I).

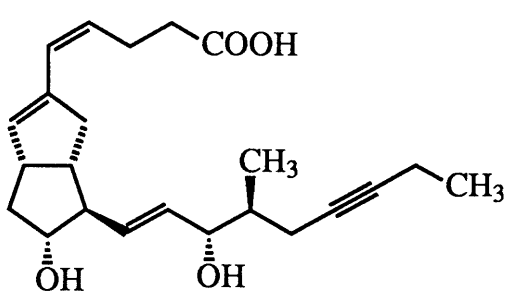
A long duration of action of an intravenously and orally active prostacyclin analogue would facilitate its clinical application. We next turned our attention to the modification of the lower side chain of **5** with short-lasting intravenous activity to improve the biological properties. We converted the 18,19-single bond into a triple bond, introduced two further methyl groups at C-16 and C-20, and selectively synthesized the pure 16*(S)*-methyl diastereomer. These modifications gave the isocarbacyclin analogue KP-10614 (**6**) with biological activities higher than those of either isocarbacyclin (**1**) or a carbacyclin analogue iloprost (**7**).[7)]



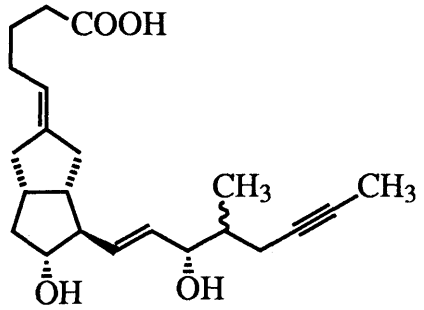
1 A = $-CH_2-$
2 A = $-O-$



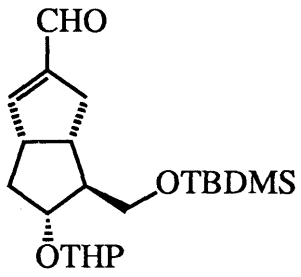
3 B = —C≡C—
4 B = —CH=CH— *(E)*
5 B = —CH=CH— *(Z)*



6 KP-10614



7 (iloprost)



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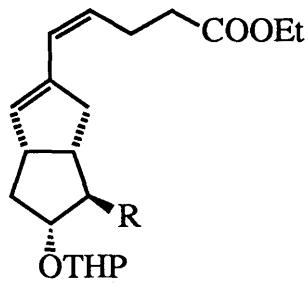
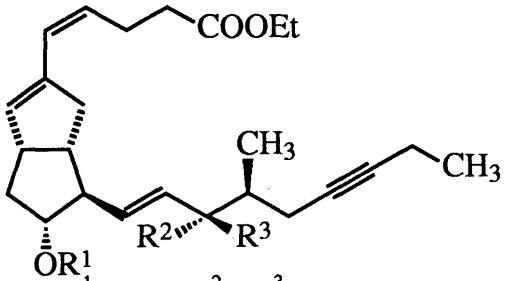
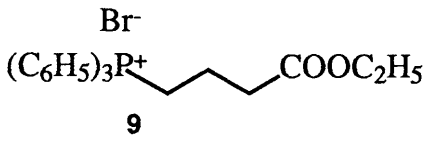


10 R = $CH_2OTBDMS$
11 R = CH_2OH
12 R = CHO



14 R^1= THP, $R^2 = R^3 = O$
15 R^1= THP, R^2 = H,OH, R^3 = OH,H
16 R^1= H, R^2 = OH, R^3 = H
17 R^1= H, R^2 = H, R^3 = OH



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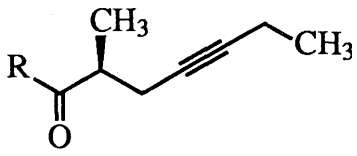

13 R = $(C_2H_5O)_2P(O)CH_2$

Table I. Effects on *in Vitro* Platelet Aggregation. IC_{50} Values for Inhibition of Human Platelet Aggregation in PRP Induced by ADP (0.8-2.0μM)

Substance	1	2	3	5	6	7	PGE_1
IC_{50}(nM)	30	100	1000	14	1	2	20

Table II. Effects on *ex Vivo* Platelet Aggregation Induced by ADP and Hypotensive Effects in Male Wistar Rats[a)]

Substance	Inhibition of platelet aggregation[b)] (intravenous infusion) ED_{50} (ng/kg/min)	Hypotensive effect[c)] (intravenous infusion) ED_{20} (ng/kg/min)	Inhibition of platelet aggregation[d)] (oral application,500μg/kg) Inhibition (%)
1	280	320	16.6
6	5	28	96.3
7	240	220	3.0

a) Rats were anesthetized with sodium pentobarbital.
b) Immediately after 15 min infusion, blood was collected from the abdominal vein.
c) The maximum reduction of arterial blood pressure during 10 min infusion was compared to the initial value.
d) Blood was collected from the abdominal vein 30 min after the oral administration.

We started the synthesis of **6** with aldehyde **8** which is readily available from the well-known Corey lactone.[8] Wittig reaction of **8** with the ylide derived from **9** and potassium *t*-butoxide in THF at -78°C afforded the *Z*-olefin **10** in 93% yield and in extremely high stereoselectivity (*Z*/*E* >98/2).[9] Treatment of **10** with $Bu_4N^+F^-$ in THF gave the alcohol **11** in quantitative yield. Oxidation of **11** with SO_3-pyridine complex and triethylamine in DMSO gave the aldehyde **12**, which was directly treated with the anion derived from the optically pure phosphonate **13**[10] and sodium hydride *in situ*. The desired enone **14** was obtained in 86% overall yield: oil; ^{1}H-NMR ($CDCl_3$)δ 0.9-1.4(9H, m), 4.08(2H, q, 7Hz, Et ester), 4.6(1H, m), 5.4(2H, m, H-4, 9α-CH), 5.88(1H, d, 11Hz, H-5), 6.5(2H, m, H-13, H-14); IR (neat) 1730, 1688, 1668, 1625cm^{-1}. Reduction of **14** with sodium borohydride in methanol at -40°C afforded the C15-epimeric alcohols **15**, which were deprotected with 65% aqueous acetic acid at 50°C for 2 h to give the more polar diol **16** in 49% overall yield together with the less polar diol **17**. Finally, hydrolysis of **16** with sodium hydroxide in aqueous methanol followed by acidic extraction provided **6** as a colorless oil in 54% yield: ^{1}H-NMR ($CDCl_3$)δ 0.95(3H, d, 6.75Hz, CH_2CH_3), 1.12(3H, t, 7.29Hz, 16ß-CH_3), 6.00(1H, d, 11.88Hz, 5-H); IR (neat) 3350, 2930, 1705cm^{-1}; MS *m/z* 354(M^+-18), 336, 259, 177, 91, 81.

Compound **6** is a potent inhibitor of platelet aggregation in human PRP (platelet rich plasma) (Table I). The inhibitory activity of platelet aggregation was also tested *ex vivo* on intravenous application in anesthetized rats. Compound **6** with ED_{50} of 5 ng/kg/min is 56-fold more potent than isocarbacyclin (**1**) and 48-fold more potent than iloprost (**7**). On the other hand, the hypotensive effect of **6** with ED_{20} of 28 ng/kg/min in the same species is 11.4-fold more potent than that of **1** and 7.9-fold more potent than that of **7** (Table II). The intravenous application of 10 μg/kg of **6** in rats shows the antiaggregatory activity lasting for >45 min (iloprost <5 min). A dose of 500 μg/kg of **6** shows 96.3% inhibition of *ex vivo* ADP-induced platelet aggregation in rats 30 min after oral administration (500 μg/kg of iloprost 3.0%).

In intravenous and oral application, **6** is superior to iloprost (**7**). Most importantly, compound **6** has a much greater separation of inhibiting platelet aggregation from hypotensive effect than either isocarbacyclin (**1**) or iloprost (**7**). In addition, **6** shows an effective activity on a cardiac infarction model in rats.[11]

ACKNOWLEDGMENT We thank Masaki Shinoda, Chiyoko Aoki, and Yuko Kimura for their excellent technical assistance.

REFERENCES AND NOTES

1) Present address: Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan.
2) S. M. Roberts and F. Scheinmann, ed., "New Synthetic Routs to Prostaglandins and Thromboxanes," pp.191-241, Academic Press, London, 1982.
3) a) M. Shibasaki, Y. Torisawa, and S. Ikegami, *Tetrahedron Lett.* , **24**, 3493 (1983);
b) M. Shibasaki, H. Fukasawa, and S. Ikegami, *Tetrahedron Lett.* , **24**, 3497 (1983).
4) a) K. Kojima, K. Koyama, S. Amemiya, and S. Saito, *Chem. Pharm. Bull.* , **34**, 948 (1987);
b) K. Kojima, S. Amemiya, K. Koyama, S. Saito, T. Oshima, and T. Ito, *Chem. Pharm. Bull.* , **35**, 4000 (1987).
5) The communication describing the conjugated diene analogues of homoisocarbacyclin was published. See: M. Shibasaki, A. Takahashi, T. Aoki, H. Sato, and S. Narita, *Chem. Pharm. Bull.* , **37**, 1647 (1989).
6) M. Shinoda, K. Iseki, T. Oguri, Y. Hayasi, S. Yamada, and M. Shibasaki, *Tetrahedron Lett.* , **27**, 87 (1986).
7) W. Skuballa and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.* , **20**, 1046 (1981).
8) M. Sodeoka and M. Shibasaki, *Chem. Lett.* , **1984**, 579.
9) K. Iseki, M. Shinoda, C. Ishiyama, Y. Hayasi, S. Yamada, and M. Shibasaki, *Chem. Lett.* , **1986**, 559.
10) W. Skuballa, E. Schillinger, C.-St. Stürzebecher, and H. Vorbrüggen, *J. Med. Chem.* , **29**, 313 (1986).
11) A more detailed description of the biological properties will be submitted for publication.

(Received March 23, 1990)