A NOVEL HOMOISOCARBACYCLIN ANALOG WITH POTENT AND LONG-LASTING ACTIVITY

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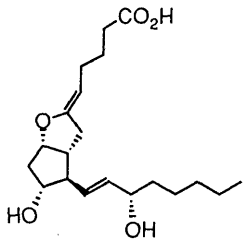
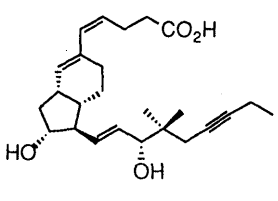
A synthesis of a novel and chemically stable homoisocarbacyclin analog, TY-11223 (3), has been accomplished. The analog (3), given intravenously or orally, showed potent and long-lasting activities in inhibiting platelet aggregation and, in addition, a good selectivity in biological activities.

KEYWORDS isocarbacyclin analog; homoisocarbacyclin analog; TY-11223; prostacyclin; iloprost; platelet antiaggregation activity; hypotensive effect

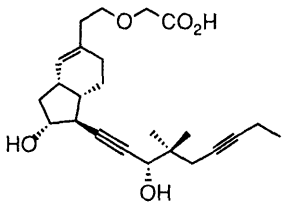
The inherent hydrolytic lability of prostacyclin limits the therapeutic use of this compound. Therefore, many efforts have been focused on the synthesis of chemically stable prostacyclin mimics during the past decade. Several analogs of those reported, such as isocarbacyclin, etc., are of great interest as therapeutic agents.[2)] We have already reported the synthesis of the novel and stable homoisocarbacyclin analog (2), which showed a biological profile similar to that of prostacyclin.[3)] It is necessary for various clinical applications of the prostacyclin analog that its platelet antiaggregation activity is potent, long-lasting and separable from hypotensive effect. We have , therefore, carried out further modifications of 2 in order to reinforce the metabolically stable property. At first, we attemped to change the upper side chain of 2. Among several modified analogs, the 3-oxapentanoic acid moiety was adopted as an upper side chain to prevent β-oxidation.[4)] The resulting decrease in intrinsic activity was made up for by modification of the lower side chain, namely, conversion of the 13-double bond into a triple bond to impede a metabolic inactivation by PG Δ^{13}-reductase.[5)] As the result, we have obtained a potent homoisocarbacyclin analog, TY-11223 (3), with outstanding long-lasting activity and a good selectivity in biological activities. In this communication, we wish to report a synthesis of this promising analog (3) and preliminary determinations of its biological activities.



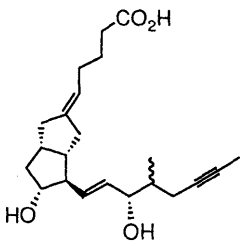
prostacyclin 1



2



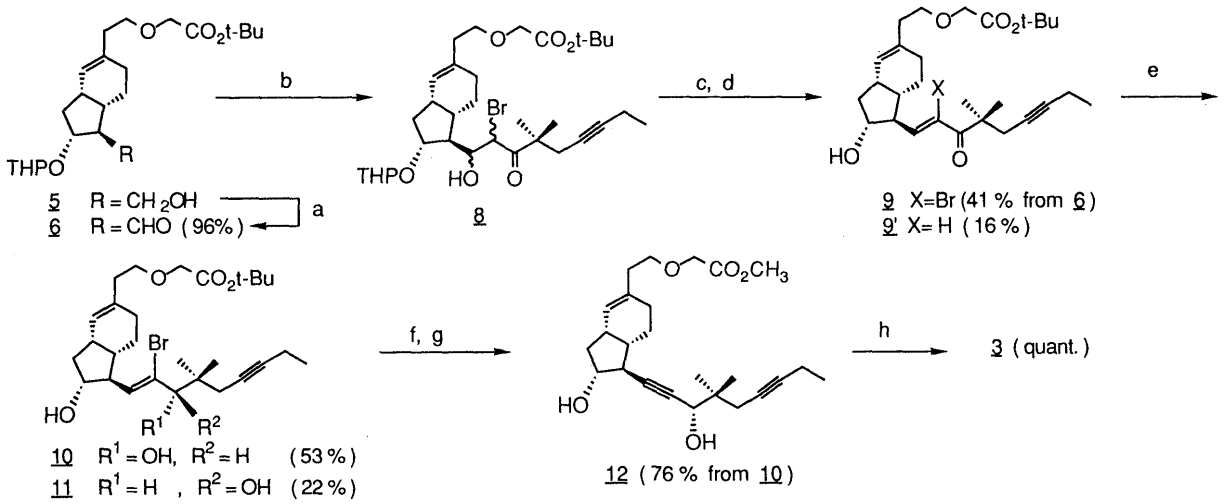
TY-11223 3



iloprost 4

The synthesis of 3 started with the versatile alcohol intermediate (5)[3)] which was readily available from the Corey lactone. Oxidation of 5 with SO_3•Py (triethylamine and DMSO) gave the corresponding aldehyde (6) in 96 % yield. Aldol condensation of 6 with α-bromo enolate anion derived from the dibromoketone (7),[6)] zinc powder and diethylaluminum chloride containing a catalytic amount of copper (I) bromide in THF at -20 °C for *ca.* 30 min provided the desired α-bromo-β-hydroxy ketone (8). Dehydration of 8 *via* the mesylate (CH_3SO_2Cl-Et_3N-DBU in CH_2Cl_2)[7)] followed by acid cleavage of the tetrahydropyranyl moiety furnished the α-bromo enone (9) in 41 % overall yield from 6 as a single stereoisomer together with the enone (9' =16 %).[8)] 9 : pale yellow oil ; ^{1}H-NMR ($CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 3H), 1.38 (s, 6H), 1.50 (s,

9H), 3.60 (t, J = 7.2 Hz, 2H), 3.95 (s, 2H), 4.10 (m, 1H), 5.42 (brs, 1H), 6.26 (d, J = 8.8 Hz, 1H) ; IR (neat) ν max 3500, 2950, 1740, 1690, 1620 cm^{-1}. Reduction of 9 with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (Yamamoto-Ono reagent) [9] in toluene at -78 °C to -20 °C for 2 h gave a diastereomeric mixture of the allylic alcohols 10 and 11, which were separated chromatographically (10 = 53 %, 11 = 22 %).[10] Dehydrobromination [50 % NaOH, n-$Bu_4N{\bullet}HSO_4$, toluene:ether (2:1), r.t.] of the desired allylic alcohol (10) with concomitant saponification of the *tert*-butyl ester group followed by esterification with diazomethane in ether for subsequent purification gave the methyl ester (12) in 76 % yield. Hydrolysis of 12 with sodium hydroxide in aqueous methanol afforded TY-11223 (3) in a nearly quantitative yield . 3 : pale yellow oil : $[\alpha]_D^{27} = +61.58°$ (c = 1.01, CH_3OH) ; ^{1}H-NMR ($CDCl_3$) δ 1.04 (s, 3H), 1.08 (s, 3H), 1.12 (t, J = 7.2 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 4.04 (s, 2H), 4.10 (m, 3H), 4.26 (d, J = 2.0 Hz, 1H), 5.38 (brs, 1H) ; IR (neat) ν max 3406, 2968, 2920, 2230, 1734, 1434, 1320 cm^{-1} ; MS m/z 403 $(M+H)^+$ (Chart 1).



(a) SO_3•Py, Et_3N, DMSO, r.t. (b) $Br_2CHC(O)C(CH_3)_2CH_2C{\equiv}CCH_2CH_3$ 7, Zn - Et_2AlCl - CuBr, THF, - 20 °C (c) MsCl, Et_3N, DBU, CH_2Cl_2, 0°C (d) TsOH, CH_3OH, r.t. (e) diisobutylaluminum 2,6-di-t-butyl-4-methylphenoxide, toluene, - 78°C～ - 20°C (f) n-$Bu_4N{\bullet}HSO_4$, 50% NaOH, toluene-ether (2:1), r.t. (g) CH_2N_2, ether, 0°C (h) 10% NaOH, CH_3OH, r.t.

Chart 1

Table I. Effects of 2, 3, 4 on *in Vitro* ADP-Induced Aggregation in Rabbit Washed Platelets [a]

Substance	2	3	4
IC_{50} (nM) [b]	4.7 ± 0.9 [c]	2.6 ± 0.7	1.5 ± 0.2

a) Aggregation was induced by 10 μM of ADP. b) Values represent mean ± SE, (n = 3). c) n = 7.

Table II. Comparison of the *ex Vivo* Effects [a] of 3 and 4 on the Inhibition of ADP-Induced Platelet Aggregation and Hypotensive Effects in Rabbits [b]

TY-11223 (3)			Iloprost (4)		
Intravenous infusion (μg/kg/min)	Inhibition of platelet aggregation [c] (%)	Hypotensive effect (mmHg) [d]	Intravenous infusion (μg/kg/min)	Inhibition of platelet aggregation [c] (%)	Hypotensive effect (mmHg) [d]
10.0	100 ± 0	- 57.9 ± 6.9	3.0	99.1 ± 0.9	- 51.4 ± 4.7
3.0	91.3 ± 8.7 [e]	- 36.1 ± 3.3 [e]	1.0	38.7 ± 18.9	- 32.8 ± 4.9
1.0	80.5 ± 19.5	- 8.8 ± 3.0	0.3	17.0 ± 19.8	- 7.6 ± 2.0

a) Values represent mean ± SE, (n = 3).
b) Rabbits were anesthetized with sodium pentobarbital.
c) During infusion for 20 min, blood was collected from the carotid artery vein 15 min after starting infusion.
d) The maximum reduction of arterial blood pressure during infusion for 20 min was compared to the initial value.
e) n = 4.

It is noteworthy that 3 is extremely stable even in an acidic aqueous ethanol solution (pH 1.2) at 40 °C.

Preliminary biological examinations indicated that 3 had a potent and long-lasting activity in inhibiting platelet aggregation and a good separation from hypotensive effect .

The analog 3 with IC_{50} value of 2.6 ± 0.7 nM was more potent than 2 (4.7 ± 0.9 nM) but less potent than iloprost (4)[11] (1.5 ± 0.2 nM) in *in vitro* inhibitory effects of ADP-induced platelet aggregation in rabbit washed platelets (Table I). On the other hand, the *ex vivo* platelet antiaggregation activity and hypotensive effect of 3 were also tested on intravenous application as compared with that of 4 in the same species. During intravenous infusion at a dose of 1 μg/kg/min, the analog 3 with 80.5 ± 19.5 % inhibition in *ex vivo* ADP-induced platelet aggregation was potent than 4 (38.7 ± 18.9 %), while *ex vivo* hypotensive effects of 3 and 4 were - 8.8 ± 3.0 mmHg and - 32.8 ± 4.9 mmHg, respectively (Table II). The analog 3 showed a greater separation from hypotensive effect than 4. [12]

The duration of *ex vivo* platelet antiaggregation activity of 3 was longer than that of 4. Namely, after the intravenous infusion of 3 at a dose of 3 μg/ kg/ min for 20 min in rabbits, the platelet antiaggregatory activity over 50 % inhibition lasted for >15 min (iloprost < 5 min). Moreover, it is worth noting that 3 exhibited >60 % inhibition of platelet aggregation in rabbits for 6 h after oral administration at a dose of 1 mg / kg. These results seem to depend on the chemically and metabolically stable property of 3.

Thus, TY-11223 (3) is a potent inhibitor of platelet aggregation with a good selectivity in biological activities. In addition, 3 has a long-lasting oral activity in inhibiting platelet aggregation, suggesting that 3 might be used for the oral route.

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6) The synthesis of 7 was done as follows : Reaction of ethyl 2,2-dimethyl-4-heptynoate[3] with lithium dibromomethylide (2.0 equiv.) in THF-ether (2 : 3) at -100 °C to -70 °C afforded the dibromoketone (7) as a pale yellow oil in 88 % yield. 7 : ^{1}H-NMR ($CDCl_3$) δ 1.01 (t, J = 8 .0 Hz, 3H), 1.28 (s, 6H), 2.04 (m, 2H), 2.30 (m, 2H), 6.32 (s, 1H) ; IR (neat) ν max 2980, 2940, 1724, 1465 cm^{-1}.

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8) The enone (9') was formed as a by-product *via* the debromination of the α-bromo-β-hydroxy ketone (8) with zinc . See ref. 7.

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10) The more polar fraction on TLC was assigned as the 15α-isomer 10 and the less polar one as the 15β-isomer, based on the known chromatographic behavior of synthetic PG intermediate.

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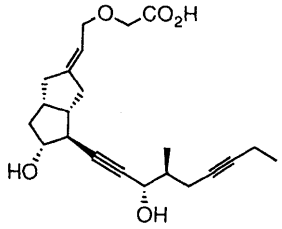
12) The Schering group had reported the synthesis and preliminary pharmacological properties of ZK 96 480 (13) as a modified analog of 4 in ref. 2f). The biological activities of 13 were described therein to be approximately 5 times more potent than that of 4. However, the selectivity of 13 in biological activities seems to be similar to those of 4. A more detailed pharmacological profile of 13 had been reported. See: S. Stürzebecher, M. Haberey, B. Muler, E. Schillinger, G. Schröde, W. Skuballa, G. Stock, H. Vorbrüggen, and W. Witt, *Prostaglandins*, **31**, 95 (1986).



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(Received October 28, 1991)