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SYNTHESES OF NEW 3-OXA-METHANO-PGI$_1$ DERIVATIVES AND THEIR BIOLOGICAL PROPERTIES

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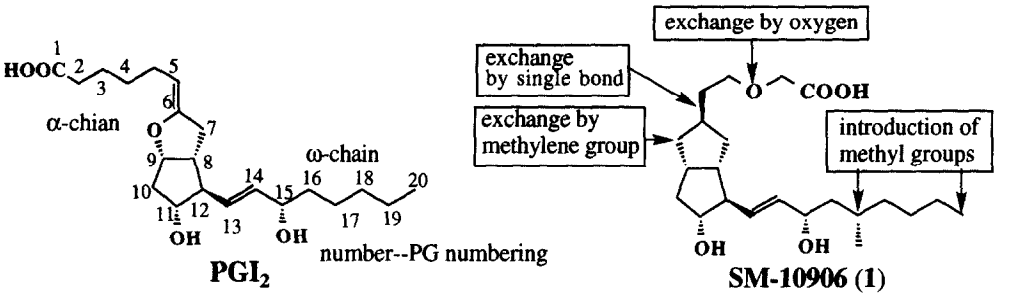
SUMMARY: Syntheses of new PGI$_1$ derivatives and inhibitory activities of blood platelet aggregation are described. It is shown that high potent 3-oxa-methano-PGI$_1$ compound SM-10906 can be obtained, when the natural α-chain is modified by introducing a 3-oxa-moiety.

INTRODUCTION AND CONCEPT: Prostacyclin (PGI$_2$)[1] is a metabolite of arachidonic acid, which shows potent platelet aggregatory inhibitory and vasodilatory action. However, due to the labile enol ether moiety and intramolecular acid catalysis by the carboxylic moiety, prostacyclin is inactivated by being rapidly hydrolyzed in the blood.[2] This limits its possible clinical application and has led to the synthesis of physico-chemically stable and biochemically potent analogues of PGI$_2$. In these approaches, many stable PGI$_2$ derivatives[3] having high biological activity were reported. The enol ether oxygen in PGI$_2$ was replaced by a methylene group, leading to potent methano-PGI$_2$ derivatives, such as Iloprost, OP-41483, Ciprostene, and Cicaprost, some of which are under clinical trials. Aza-PGI$_2$ derivatives, such as OP-2507, which incorporate an imino group, 5-cyano PGI$_2$ derivative, such as Nileprost, and benzo-PGI$_2$ derivatives, such as Beraprost and Taprostene, are also potent PGI$_2$ analogues. On the other hand, when the enol ether double bond in PGI$_2$ was replaced by a single bond, the PGI$_1$ derivatives were remarkably less potent than PGE$_1$ or PGI$_2$ in inhibiting the aggregation of blood platelets though physico-chemically stable. For example, exo-PGI$_1$ and endo-PGI$_1$ were respectively 20 and 400 times less potent than PGE$_1$,[3] and methano-PGI$_1$ was 80 times less potent than PGE$_1$.[4]
In our preliminary approaches, we tried to modify the methano-PGI$_1$ to increase the activity as well as physico-chemical and metabolic stability by introducing a heteroatom into the natural α-chain of PGs, and found that the 3-oxa-methano-PGI$_1$ derivatives were substantially more potent than 4-oxa, 5-oxa-methano-PGI$_1$ derivatives[5] and 3-thia-methano-PGI$_1$ derivatives[6] in inhibitory activities of blood platelet aggregation. Further structural modification to increase the activity concentrated on the ω-chain of PGs and resulted in the synthesis of 3-oxa-17S,20-dimethyl-methano-PGI$_1$(**1**, **SM-10906**),[7] which was the most potent compound of the 3-oxa-methano-PGI$_1$ derivatives . In this report, we describe synthetic procedures and biological activities of the 3-oxa-methano-PGI$_1$ derivative **1** and its isomers.

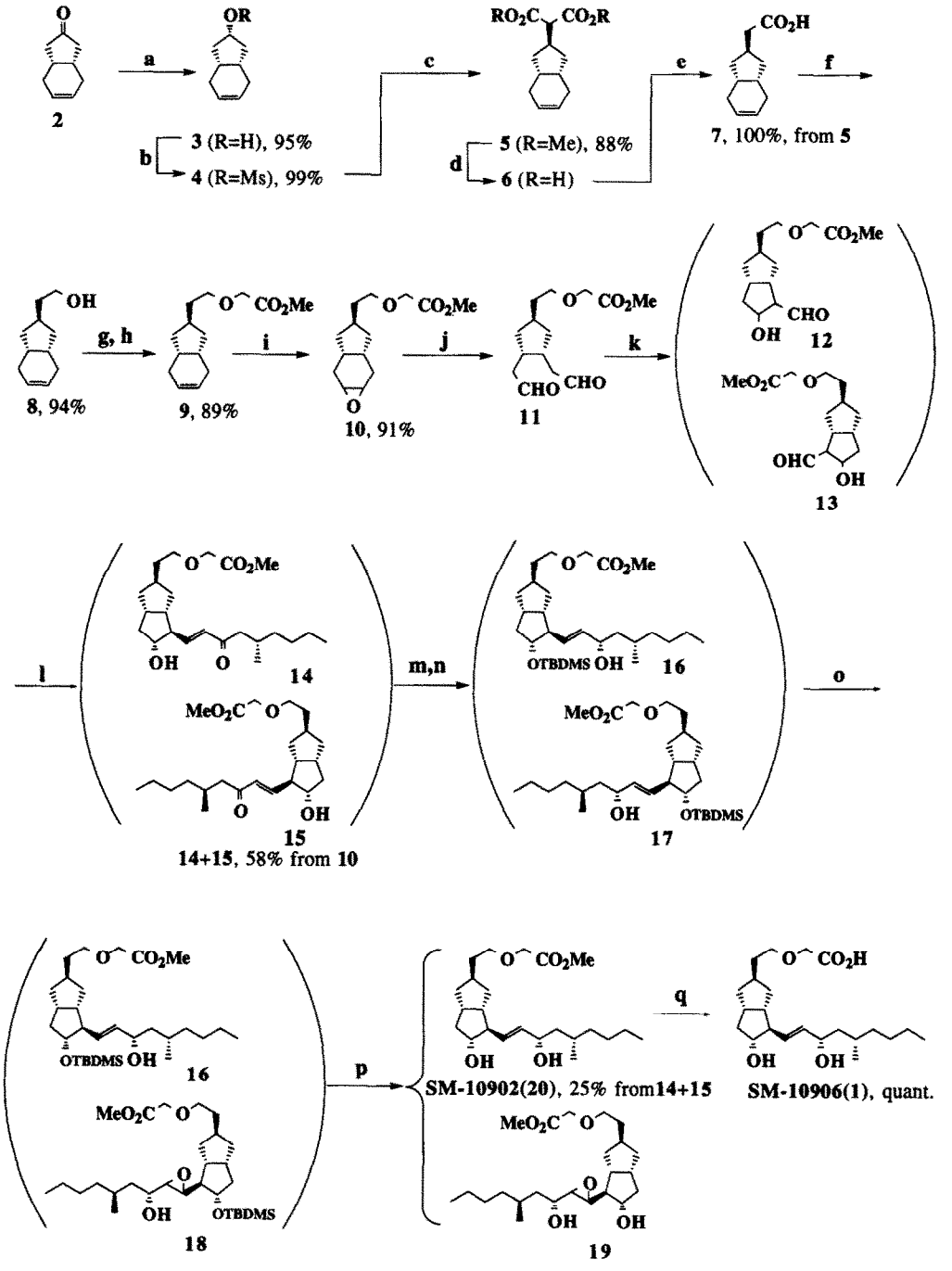
Stucture feature of SM-10906 in comparison with PGI_2



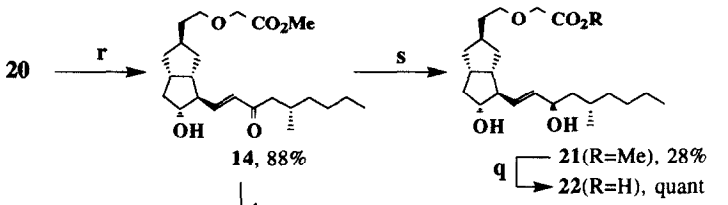
SYNTHESIS: Starting from the easily available ketone **2**, we reduced the carbonyl group of **2** with Red Al under mild conditions (-65°C), resulting in α-alcohol **3** containing a small amount of β-alcohol (ca. 4%), which could be removed later. Mesylation of **3**, followed by alkylation of mesylate with malonate, saponification of the diester **5** with KOH, and decarboxylation under reflux in xylene gave 3-β-carboxylic acid **7** (mp 52-53°C). A small amount of 3-α-carboxylic acid in the resultant acid **7** could be completely removed by repeated recrystallization from hexane. Reduction of **7** with Red Al, followed by alkylation with sodium chloroacetate and esterification gave the key intermediate **9**. Epoxidation of the olefin in **9** in a two phase reaction system with hydrogen peroxide, alkali tungstate and phosphoric acid in the presence of quarternary ammonium salt, followed by ring-cleavage of the epoxide ring in **10** with periodic acid gave the labile dialdehyde **11**. Aldol condensation of dialdehyde **11** in the presence of piperidine and acetic acid for 10 min and immediate Wittig-Horner reaction with dimethyl 4S-methyl-2-oxooctylphosphonate, followed by purification by chromatography gave a nearly 1:1 mixture of **14** and **15**, which could not be separated by HPLC. After protection of the C-11 hydroxyl group in the mixture of **14** and **15** with TBDMSCl, reduction with $NaBH_4$ in the presence of $CeCl_3$[8] at -45°C gave a mixture of 15-α-alcohols **16** and **17**, and a small amount of their 15-β-isomers (84%yield, α/β=9/1).[9] The mixture of 15-α-alcohol **16** and **17** could be easily separated from their 15-β-isomers by chromatography. Though the desired alcohol **16** could not be separated by HPLC from **17**. Therefore, we applied the Sharpless epoxidation for the purpose of effective isolation of **16** from **17**. Sharpless epoxidation[10] of the mixture of **16** and **17** in the presence of (-)-DIPT, followed by deprotection gave the mixture of desired **20** and epoxide **19**. Desired **20** could be easily separated from **19** by chromatography. The absolute configuration of **20** was confirmed by ^1H NMR and ^{13}C NMR spectroscopy employing, Mosher's method[11] and line width method, and further supported by exciton coupled circular dichromic spectroscopy, and the configuration of the starting material **2**.[12] Saponification of **20** with NaOH furnished **SM-10906 (1)**.

The epimers of **1** were produced by the following procedures: Oxidation of **20** with MnO_2, followed by reduction with $NaBH_4$ gave a mixture of alcohol **20** and **21** which were readily separated by chromatography. Saponification of the ester **21** with NaOH furnished **22**, the 15-epimer of **1**. Mitsunobu reaction[13] of the alcohol group at the position 11 in enone **14**, followed by reduction with $NaBH_4$ gave a mixture, which were readily separated by chromatography to give the ester **24**. Saponification of the ester **24** with NaOH furnished **25**, the 11-epimer of **1**. Wittig-Horner reaction of the mixture of **12** and **13** with dimethyl 4R-methyl-2-oxo-octylphosphonate, followed by reduction with L-Selectride gave the mixture of alcohols, which were separated by HPLC to give the ester **28**. Saponification of the ester **28** with NaOH furnished **29**, the 17-epimer of **1**.

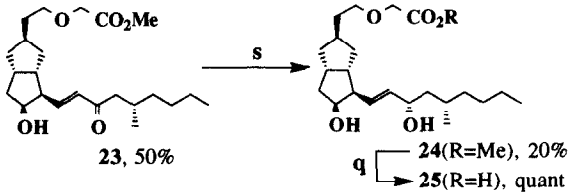
Synthesis of SM-10906



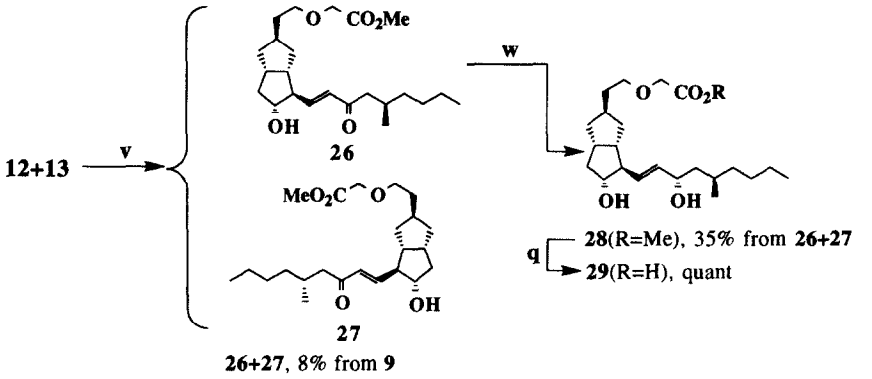
Synthesis of 22



Synthesis of 25



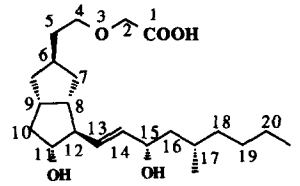
Synthesis of 29



CONDITIONS: **a**: Red Al, toluene, -65°C, 2hr; **b**: MsCl, triethylamine, toluene, 10°C, 1hr; **c**: NaH, dimethylmalonate, toluene, MeOH, 65°C, 3hr; **d**: 20%KOH, IPA, 80°C, 3hr; **e**: xylene, reflux, 5hr; **f**: Red Al, toluene, 45°C, 2hr; **g**: n-BuLi, DMSO, $ClCH_2CO_2Na$, 50°C, 5hr; **h**: MeOH, c-H_2SO_4, 20°C, 15hr; **i**: H_2O_2, Na_2WO_4, 85% H_3PO_4, CH_2Cl_2, H_2O, cetyltrimethylammonium bromide, 72°C, 5hr; **j**: HIO_4, CH_2Cl_2, H_2O, 25°C, 4hr; **k**: piperidine, acetic acid, -5°C, 10min; **l**: NaH, dimethyl 4S-methyl-2-oxooctylphosphonate, THF, rt, 2hr, SiO_2; **m**: TBDMSCl, imidazole, DMF, rt, 5hr; **n**: $NaBH_4$, $CeCl_3$,[8] EtOH, -45°C, 8hr; **o**: (-) DIPT, Ti(Oi-Pr)4, TBHP, -20°C, 15hr; **p**: AcOH/MeOH/H_2O=1/3/1, rt, 12hr, SiO_2 ; **q**: 1N-NaOH, MeOH, 0°C, 30min; **r**: MnO_2, chloroform, rt, 2hr, SiO_2; **s**: $NaBH_4$, MeOH, 0°C, 30min, SiO_2; **t**: Ph_3P, HCO_2H, DEAD, THF, rt, 10hr; **u**: K_2CO_3, MeOH, rt, 2h, SiO_2; **v**: NaH, dimethyl 4R-methyl-2-oxooctylphosphonate, THF, rt, 2hr, SiO_2 ; **w**: L-Selectride, THF, -60°C, 30min, SiO_2.

RESULTS : The biological data of PGI_1 derivatives synthesized above are given in *Table 1*,[14,15] in which their inhibitory activities of blood platelet aggregation[16] in rabbit platelet-rich plasma stimulated by ADP were compared with PGE_1 as standard. As depicted in *Table 1*, the activity of **1, SM-10906** was nearly equipotent with PGE_1 and was remarkably enhanced in comparison with known PGI_1 derivatives owing to introduction of 3-oxa moiety into natural α-chain.[5] On the other hand, both PGI_2 analogue, Iloprost and its 3-oxa-PGI_2 derivative, Z96480 were high potent.[17] **1** was 70 times more potent than methano-PGI_1. (compound **1, A** and **B**). As was expected in general,[18] the stereoisomers of **1** were less potent compared with **1**. For example, the 11-epimer and 15-epimer were over 300 times less potent than **1** and the 17-epimer was 3 times less potent (compound **1, 25, 22** and **29**). In *Table 2* and *Table 3*,[19] the platelet aggregation inhibitory activities of **1** induced by some aggregating agents in platelet-rich plasma of different species are provided. The agent **1** inhibited platelet aggregation induced by collagen and arachidonic acid as well as ADP and inhibited platelet aggregation in platelet-rich plasma of human, guinea-pig, dog and rat as well as rabbit. **SM-10902 (20)**, which is a pro-drug of **SM-10906 (1)**, is now under clinical study .

Table 1 **Biological activities of SM-10906 and its isomers**
inhibition of rabbit blood platelet aggregation induced by ADP



SM-10906

compound		relative activity
1	SM-10906	1 / 1.2
25	SM-10906, 11-epi	< 1 / 400
22	SM-10906, 15-epi	< 1 / 400
29	SM-10906, 17-epi	1 / 3.6
A	PGE_1	1
B	methano-PGI_1[4]	1 / 80

Table 2 **Biological activities of SM-10906 in various species**
inhibition of ADP-induced platelet aggregation (IC_{50}, ng/ml)

Species	SM-10906	PGE_1
Human	12.5 ± 2.7	13.6 ± 2.7
Guinnea-pig	3.1 ± 0.5	2.5 ± 0.3
Dog	4.3 ± 0.7	3.8 ± 0.8
Rat	9.8 ± 0.7	34.4 ± 5.1
Rabbit	24.1 ± 4.6	20.7 ± 5.7

Table 3 **Biological activity of SM-10906 with various aggregating reagents**
inhibition of rabbit platelet aggregation (IC_{50}, ng/ml)

aggregating reagent	SM-10906	PGE_1
ADP	24.1 ± 4.6	20.7 ± 5.7
collagen	18.3 ± 4.4	13.2 ± 2.6
arachidonic acid	47.6 ± 4.7	35.9 ± 3.8

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