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A Simple Stereoselective Synthesis and Biological Evaluation of FR181157: Orally Active Prostacyclin Mimetic

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Abstract—Synthetic method of novel prostaglandin (PG) mimetic: FR181175 without PG skeleton are described. The key to success is creation of a chiral epoxide using Sharpless AD reaction with high ee yield. FR181157 shows high potency and agonist efficacy at the IP receptor and has good bioavailability.

Introduction

Prostacyclin (PGI_2): **1** is primarily derived from vascular endothelium and plays an extremely important inhibitory role in platelet aggregation and as a vasodilator in maintaining homeostatic circulation.[1] Despite fascinating pharmacological properties, the inherent instability of **1** limits its therapeutic applicability. An Edinburgh University group,[2] a Bristol-Myers Squibb group,[3] and an Ono group[4] has already disclosed novel PGI_2 analogues without a PG skeleton. These investigation led us to create of novel PGI_2 mimetic with improved on both chemical and metabolic stability. After extensive research, we found the non prostanoid structure FR181157: (*S*)-**4** having potent PGI_2 activity with improved pharmacokinetic property. In order to generate multigram quantities of (*S*)-**4** for continuing biological evaluation and its toxicity, an efficient synthetic route had to be developed. In this paper, we would like to describe a practical and simple stereoselective synthesis and biological activity of (*S*)-**4** (Fig. 1).

Chemistry

Our synthetic strategy is illustrated in Scheme 1. We address to make this compound by especially controlling stereochemistry at a benzyl center and a double bond of a cyclohexene ring. The key substrate that was the focus for construction of the desired stereochemistry of **4** was a chiral epoxide. A ring opening of the epoxide by a nucleophile creates a chiral center at the benzyl position and hydroxyl function favorable arranged for the control of an *exo*-olefin in the process of elimination.[5]

The required optically active epoxide **8** was obtained via the Sharpless AD reaction and epoxidation shown in Scheme 2. Commercially available 1-cyclohexenylcarboxylic acid **5** was easily transformed into 1-cyclohexenyloxazole **6** by condensation with benzoin followed by treatment with ammonium acetate in acetic acid. Asymmetric dihydroxylation of **6** by the standard procedure[6] with 1 mol% of AD-mix-α provided the diol

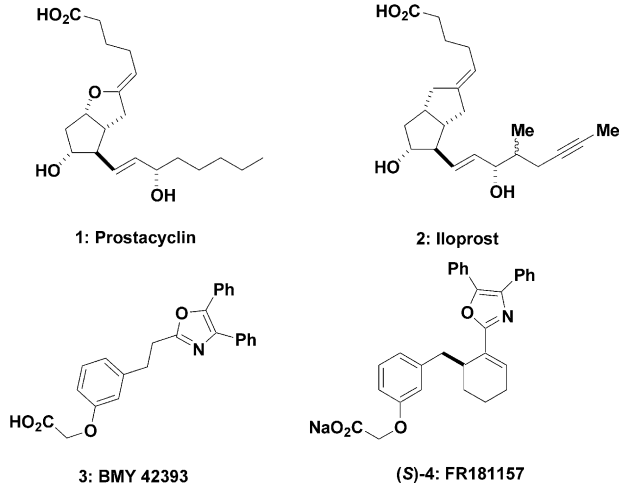

Figure 1.

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7 in 98% ee. Treatment by crystallization with hexane-ether gave the optically pure product in 80% yield and >99% ee as determined by HPLC analysis with a chiral column (Chiralcel AD). The diols **7** was smoothly converted to the epoxide **8** using the method involving a cyclic acetoxonium intermediate.[7] The key chiral epoxide **8** was effectively produced on 100–300 g scale without any purification by column chromatography.

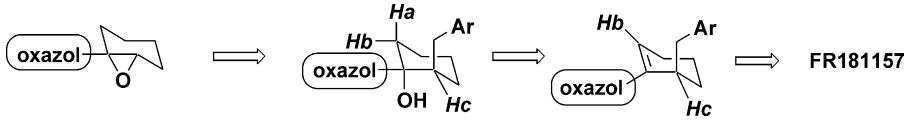
The completion of the synthesis of (*S*)-**4** from **8** was accomplished by the route outline in Scheme 3. Ring opening of **8** with methoxybenzylmagnesium chloride (5 equiv) in the presence of a catalytic amount of CuBr provided quantitatively the alcohol compound **9** after purification of short column chromatography. Elimination of water successfully proceeded with the predicted regioselectivity upon treatment with *p*-toluenesulfonic acid (0.2 equiv) under toluene azeotrope. The crude product was purified by crystallization from hexane–ether to obtain the *exo*-olefin **10** as a single isomer in 64% yield and >99% ee (as determined by HPLC). This reaction gave the olefin compounds with a ratio of *exo*/*endo* = 90:10.[8] The regioselectivity of the obtained olefin compounds may be controlled under kinetic control. When the *exo*-olefin was treated with *p*-toluenesulfonic acid under toluene azeotrope, we could not observe isomerization to the *endo*-olefin. On the other hand, the treatment of the *endo*-olefin isolated by column chromatography with the same condition could not also occur isomerization. These results suggest that olefin are not prone to rapid equilibration. Enantiomerically pure **10** was subsequently treated with BBr_3 followed by alkylation with ethylbromoacetate gave the ethyl ester **13**. Finally, hydrolysis of **13** furnished (*S*)-**4** in 81% yield and >99% ee from **10**.[9]

Table 1. In vitro effect of FR181157 and the derivatives

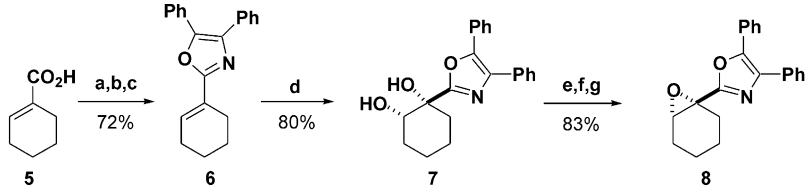
	Function assay (IC_{50} nM)	Binding assay (K_i nM)
(*S*)-**4**: FR181157	60	54
(*R*)-**4**	110	NT
14	530	NT
3: BMY 42393	3400	NT
2: Iloprost	2.5	6.5

Biological activity

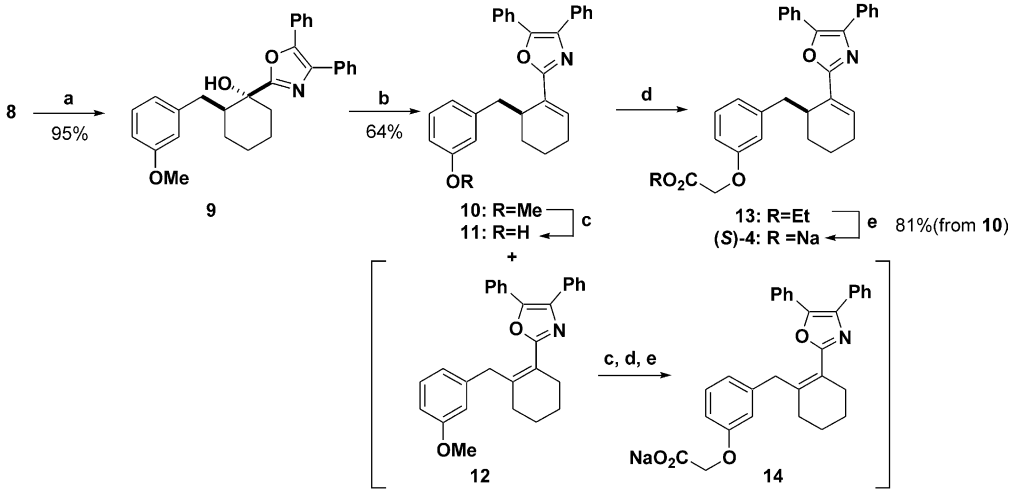
FR181157 possesses potent PGI_2 agonist activity and especially good pharmacokinetic properties. Table 1 was shown the in vitro activity. PGI_2 receptor binding was examined by the conventional ligand binding assay



Scheme 1.



Scheme 2. (a) $SOCl_2$, CH_2Cl_2; (b) benzoin, Et_3N, CH_2Cl_2; (c) $AcONH_4$, AcOH; (d) AD-*mix*-α, ^tBuOH–H_2O; (e) $Me(OMe)_3$, cat. *p*-TsOH, CH_2Cl_2; (f) AcBr, CH_2Cl_2; (g) K_2CO_3, MeOH.



Scheme 3. (a) *m*-MeOBzMgBr, cat. CuBr, THF; (b) cat. *p*-TsOH, Tol; (c) BBr_3, CH_2Cl_2; (d) $BrCH_2CO_2Et$, K_2CO_3; DMF; (e) NaOH, EtOH.

Table 2. Pharmacokinetics profiles of FR181157

	(po, fasted)				(iv)		*F* (%)
	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng h/mL)	$t_{1/2}\beta$ (h)	CL_{tot} (mL/min/kg)	
Rat	0.32	16.4	0.3	147.0	6.6	17.7	50
Dog	0.032	38.7	2.3	391.7	26	1.09	72

based on the displacement of [^{3}H]-Iloprost from the cloned human IP receptor.[10] IC_{50} values of the functional assay was obtained by measuring inhibition of ADP-induced platelet aggregation using human platelet rich plasma. FR181157 exhibited high binding affinity for the IP receptor with a K_i of 54 nM and anti-aggregative potency with an IC_{50} of 60 nM. The enatiomer isomer (*R*)-**4** was 2-fold less potent, and also the *endo*-olefin **14** was 9-fold less potent under the same condition. It is well known that this class of PGI_2 mimetic has species difference.[1] FR181157 was also observed the same result, inhibition of ADP-induced platelet aggregation using rat and dog platelet rich plasma was 20-fold less potent than human (rat: $IC_{50} = 1.2$ μM, dog: $IC_{50} = 1.3$ μM). Table 2 was shown the pharmacokinetic profiles of rat and dog. FR181157 without a PG skelton displayed a good oral bioavailability (rat: F = 50%, dog: F = 72%) and long duration time in the both species. The detailed pharmacological and pharmacokinetic properties of FR181157 will be published in future.

Conclusion

In this communication, we have reported an operationally simple method for the highly stereoselective synthesis and a biological evaluation of FR181157, a potent and orally active prostacylin mimetic. This is a 12-step synthesis from commercially available starting materials, and involves only simple purification to give a 100-g scale. This route should be suitable for industrial order.

Acknowledgements

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8. The ratio of the crude product was determined by ^{1}H NMR. *endo*-Olefin was completely removed by crystallization. ^{1}H NMR of benzyl proton in $CDCl_3$, **10**: δ 2.53 (1H, dd, $J = 10.2$, 12.8 Hz), 2.31 (1H, dd, $J = 3.2$, 12.8 Hz), **12**: δ 4.09 (2H, s).
9. The assignment of the absolute configuration of FR181157 was determined by X-ray structural analysis. (*S*)-**4** $[\alpha]_D^{24}$ +93.0 (*c* 0.20, MeOH); HPLC (chiralcel AGP, 10 cm×0.4 cm I.D., flow rate 0.8 mL/min, 20% acetonitrile/0.02 M phosphate buffer) $R_t = 4.0$ min (>99%). [(*R*)-**4**: $R_t = 6.0$ min]. This compound should be handled with extreme caution because of PGI_2 agonist activity and high permeability of skin.
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