Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 1743–1759

BIOORGANIC & MEDICINAL CHEMISTRY

Design and Synthesis of a Selective EP4-Receptor Agonist. Part 3: 16-Phenyl-5-thiaPGE$_1$ and 9-β-Halo Derivatives with Improved Stability

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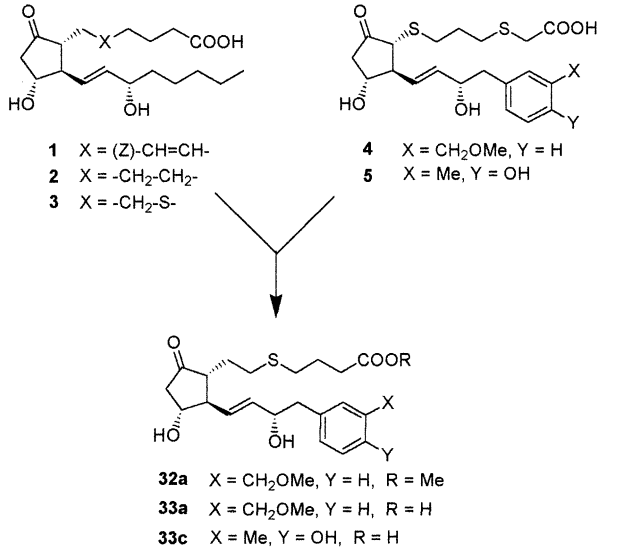
Received 7 November 2001; accepted 12 January 2002

Abstract—To identify a new selective EP4-agonist with improved chemical stability, further chemical modification of those reported previously was continued. We focused our attention on chemical modification of the α chain of 3,7-dithiaPGE$_1$ and selected 5-thiaPGE$_1$ as a new chemical lead. Introduction of an optimized ω chain to the 5-thiaPG skeleton afforded *m*-methoxymethyl derivative **33a**, which showed the most potent EP4-receptor agonist activity and good subtype-selectivity both in vitro and in vivo. 9β-HaloPGF derivatives were also synthesized and biologically evaluated in an attempt to block self-degradation of the β-hydroxy-ketone moiety. Among these series, **39a** and **39b** showed potent agonist activity and good subtype-selectivity. Structure–activity relationships (SARs) are also discussed.

Introduction

Stimulation of the EP4-receptor by PGE$_2$ leads to an increase in intracellular cAMP level, which has been suggested to be coordinated with the cytoprotective activity of PGE$_2$ such as a protection of the organs and/or tissues from damage.[1] The above biological activities are considered to be due to the improvement of blood flow and the modulation of inflammatory cytokine generation.[2] Identification of a highly selective EP4-receptor agonist, which is chemically stable, would contribute not only to determination of the biological role of the EP4-receptor but also to development of clinically useful drugs without side effects such as constriction of the uterus. Identification of 3,7-dithiaPGE$_1$ with a 16-phenyl ω chain followed by further optimization of the ω chain were reported previously.[3] As a result, 16-(*m*-methoxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ **4** was identified as the most optimized EP4-receptor selective agonist. To develop a highly selective EP4-receptor agonist as a clinically useful drug, the chemical instability due to the β-hydroxy ketone moiety and the easily enolizable structure of the 3,7-dithia partial structure[4] remains to be solved. To search for a more chemically stable structure, we continued further chemical modification of the α chain maintaining the optimized ω chain. More chemically stable 16-phenyl-ω-tetranor-5-thiaPGE$_1$ derivatives were identified (Scheme 1),



Scheme 1. Discovery of 16-phenyl-ω-tetranor-5-thiaPGE$_1$ as highly selective EP4-receptor agonists **32a**, **33a** and **33c**.

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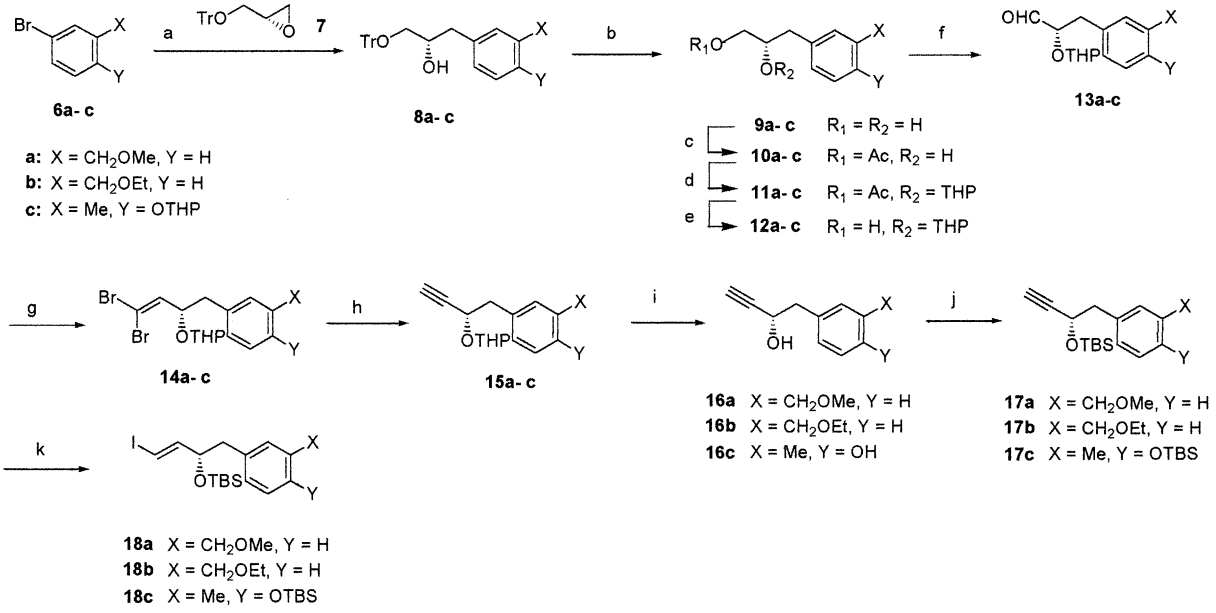
0968-0896/02/$ - see front matter
PII: S0968-0896(02)00031-7

and their structure–activity relationships (SARs) are discussed.

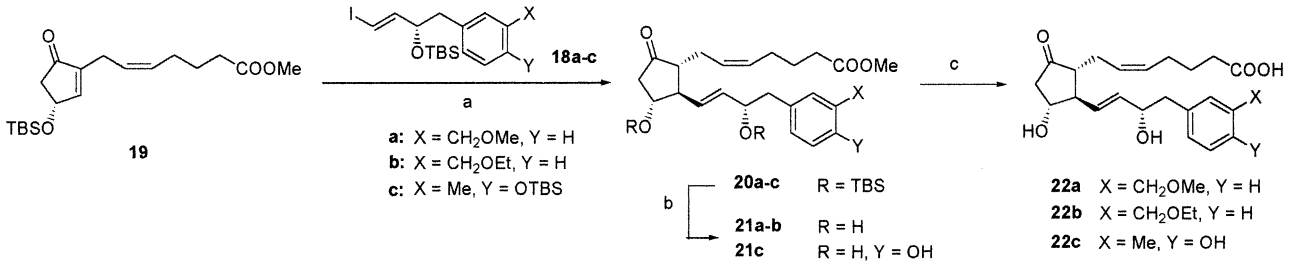
Chemistry

The preparation of optically active vinyl iodides **18a–c** is described in Scheme 2. Aryl bromides **6a–c** were converted to the corresponding Grignard reagents. Ring opening reaction of epoxide **7** with these Grignard reagents afforded **8a–c**, respectively. Removal of the trityl group of **8a–c** under acidic conditions, followed by selective acetylation reported by Yamamoto[5] provided **10a–c**. After selective protection of the secondary alcohol of **10a–c** as a tetrahydropyranyl (THP) ether, the acetyl group was removed by hydrolysis to give alcohols **12a–c**. Oxidation of **12a–c** afforded the corresponding aldehydes **13a–c**, which were converted to alkynes **15a–c** by the method reported by Corey.[6] After removal of the THP group in **15a–c**, reprotection of the resulting hydroxy group as a *t*-butyldimethylsilyl (TBS) ether provided **17a–c**. Alkynes **17a–c** were converted to the corresponding vinyl iodides **18a–c** in good yield.[7]

Syntheses of the PGE analogues **22a–c**, **26a–c**, **33a**, **33c** are outlined in Schemes 3–5. As described in Scheme 3, Michael addition of the lithiated olefins, which were prepared from the corresponding vinyl iodides **18a–c**, to the enone **19**[8] provided **20a–c**, the TBS group of which was removed under acidic conditions to afford **21a–c**. Chemicoenzymatic hydrolysis of **21a–c** in phosphate buffer provided **22a–c**. According to the same procedures as described in Scheme 3, compound **23** was converted to **26a–c** as shown in Scheme 4. Synthesis of **33a** and **33c** was accomplished by the three-component coupling process[9,10] as described in Scheme 5. Michael addition of the vinyl iodide **18a** and **18c** to the enone **27** followed by trapping of the formed enolate anion with the aldehyde **28** afforded β-hydroxyketones **29a** and **29c**. Methanesulfonylation followed by elimination of the hydroxy group of **29a** and **29c** provided **30a** and **30c**, hydrogenation of which was carried out by tri-*n*-butyltin hydride reduction to afford **31a** and **31c**, respectively. Deprotection of TBS ether was simultaneously performed under acidic conditions to give **32a** and **32c**, and then their chemicoenzymatic hydrolysis provided **33a** and **33c**, respectively. Synthesis of 9β-haloPGF



Scheme 2. Preparation of optically active vinyl iodide **18a–c**. Reagents: (a) Mg, CuI, THF then **7**; (b) AcOH, THF, H_2O; (c) AcCl, 2,4,6-collidine, CH_2Cl_2; (d) DHP, *p*-TsOHH_2O, CH_2Cl_2; (e) 2 N NaOH, MeOH; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (g) CBr_4, Ph_3P, Et_3N, CH_2Cl_2; (h) *n*-BuLi, THF; (i) 4 N HCl–dioxane, MeOH; (j) TBSCl, imidazol, DMF; (k) Cp_2ZrClH, I_2, THF.

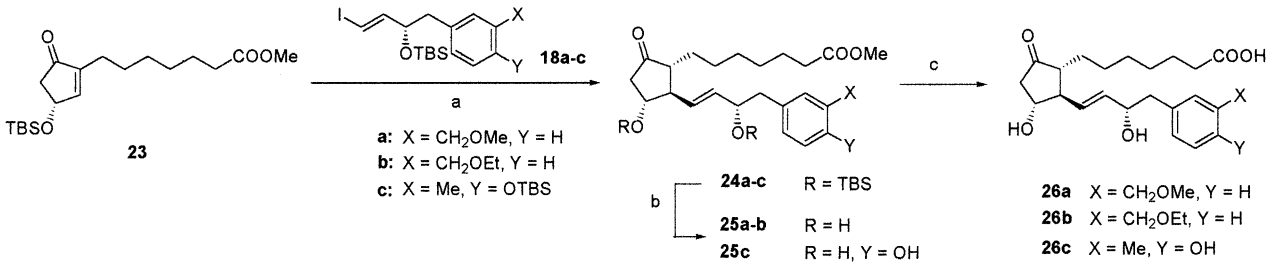


Scheme 3. Synthesis of **22a–c**. Reagents: (a) **18a–c**, *t*-BuLi, lithium (2-thienyl)cyanocuprate, ether, THF; (b) $(HF)_n$-Py, pyridine, CH_3CN; (c) PLE, EtOH, phosphate buffer.

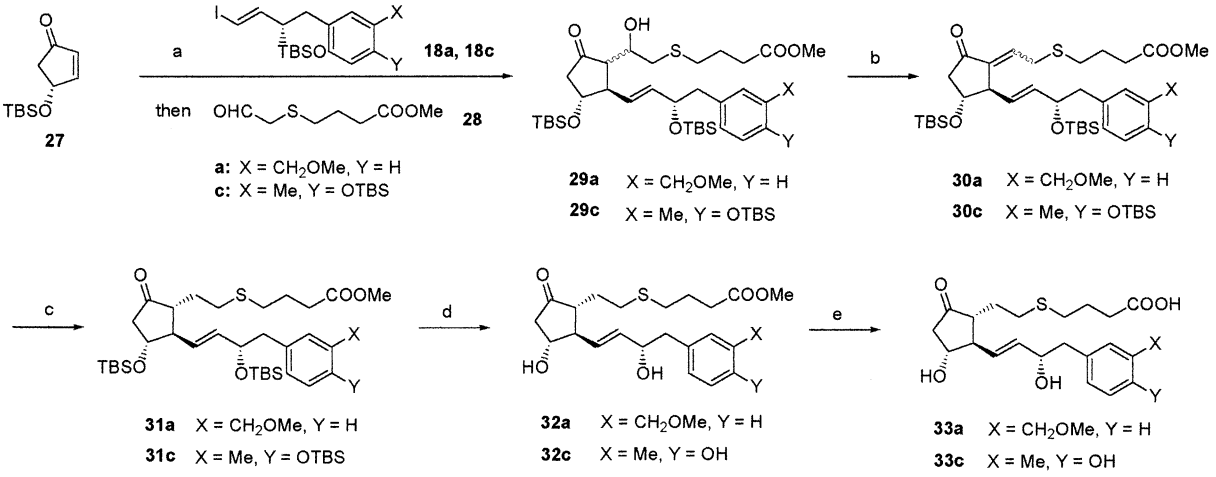
analogues is outlined in Schemes 6–8. Stereoselective reduction of **20a–c** with lithium tri-*s*-butylborohydride[11] produced **34a–c**, tosylation of which afforded **35a–c**. Substitution reaction of **35a–c** with tetrabutylammonium chloride[12] (TBACl) and tetrabutylammonium fluoride[12] (TBAF) provided **36a–c** and **37a**, respectively. Acid deprotection of **36a–c** and **37a** followed by alkaline hydrolysis afforded **39a–c** and **41a**. According to the same procedures as described in the synthesis of **39a–c**, **46a** and **46c** were prepared from **24a** and **24c**, respectively (Scheme 7). According to the same procedures as described in the synthesis of **41a**, **51a** was prepared from **47**, preparation of which is briefly described in the Experimental (Scheme 8).

Results and Discussion

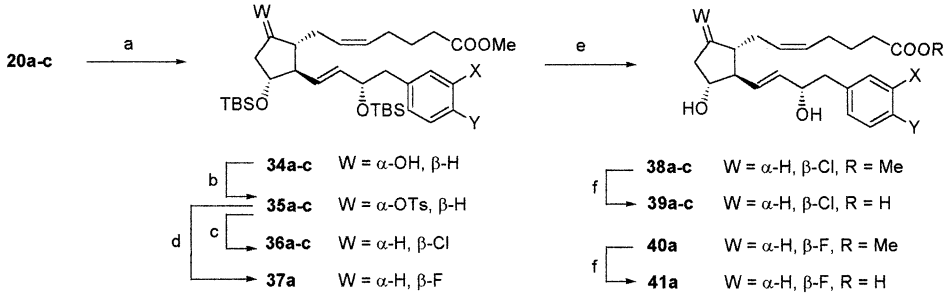
Introduction of a sulfur atom or atoms into the α chain of PGE_1 was discovered to increase the EP4-receptor selectivity and agonist activity. Chemical modification of the ω chain of 3,7-dithiaPGE_1 was continued to further improve the EP4-receptor selectivity and agonist activity. Among the compounds tested, **4** showed a good profile as a potent and selective EP4-receptor agonist. Binding assay was conducted according to the reported method[13] with minor modifications. The binding constants (K_i values) were determined by competitive binding assay of the test compounds using radiolabeled ligands such as [^{3}H]PGE_2 (EP-receptors) and [^{3}H]Iloprost (IP-receptor).



Scheme 4. Synthesis of **26a–c**. Reagents: (a) **18a–c**, *t*-BuLi, lithium (2-thienyl)cyanocuprate, ether, THF; (b) $(HF)_n$·Py, pyridine, CH_3CN; (c) PLE, EtOH, phosphate buffer.



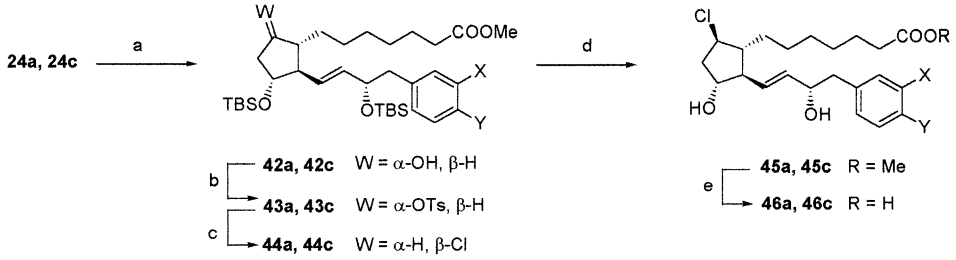
Scheme 5. Synthesis of **33a** and **33c**. Reagents: (a) **18a** or **18c**, *t*-BuLi, lithium (2-thienyl)cyanocuprate, ether, THF then **28**; (b) MsCl, DMAP, CH_2Cl_2; (c) *n*-Bu_3SnH, $(tBuO)_2$; (d) $(HF)_n$·Py, pyridine, CH_3CN; (e) PLE, EtOH, phosphate buffer.



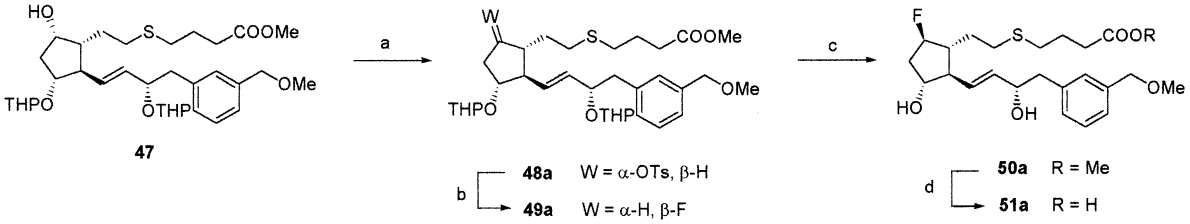
Scheme 6. Synthesis of 9β-haloPGE_2 analogues **39a–c** and **41a**. Reagents: (a) lithium tri-*s*-butylborohydride, THF; (b) *p*-TsCl, pyridine, DMAP; (c) TBACl, K_2CO_3, toluene; (d) TBAF, K_2CO_3, toluene; (e) *p*-TsOH, MeOH; (f) 1 N NaOH, MeOH.

Functional assay was conducted as follows. The intracellular Ca^{2+} increase using CHO cells expressing EP3-receptors was measured to estimate the EP3-receptor agonist activity. The intracellular cAMP production in CHO cells expressing EP4-receptors was measured to estimate the EP4-receptor agonist activity.

To search for chemically stable and selective EP4-receptor agonists, we started our molecular design with modification of the α chain of 7-thiaPGE$_1$ **52**[9] because of its potent EP4-receptor affinity. One of the reasons for the instability of the series of 3,7-dithiaPGEs is their ready enolizability based on their α-alkylthiaketone structure.[4] To avoid the '7-thiaPGE' structure, our chemical modifications started with transfer of the sulfur atom from position 7 to position 6, 5, 4 or 3 to afford **53**, **3**, **54** and **55**, respectively.[9] As outlined in Table 1, the EP4-receptor selectivity was nearly restored in

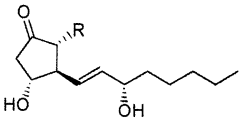


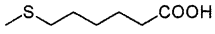
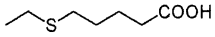
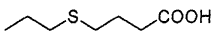
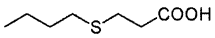
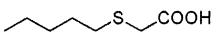
Scheme 7. Synthesis of 9β-chloroPGE$_1$ analogues **46a** and **46c**. Reagents: (a) lithium tri-*s*-butylborohydride, THF; (b) *p*-TsCl, pyridine, DMAP; (c) TBACl, K_2CO_3, toluene; (d) *p*-TsOH, MeOH; (e) 1 N NaOH, MeOH.



Scheme 8. Synthesis of 9β-fluoro-5-thiaPGE$_1$ analogue **51a**. Reagents: (a) *p*-TsCl, pyridine, DMAP; (b) TBAF, K_2CO_3, toluene; (c) *p*-TsOH, MeOH; (d) 1 N NaOH, MeOH.

Table 1. Biological evaluation of thia and oxaPGE$_1$ congeners **3** and **52**–**55**



Compound	R	Binding K_i (nM)					EC_{50} (nM)
		mEP1	mEP2	mEP3	mEP4	hIP	mEP4
52		120	100	4.5	0.7	870	3.7
53		95	91	2.0	8.7	1400	1000
3		52	75	1.9	0.5	750	3.6
54		27	340	3.7	11	920	1000
55		200	49	1.2	2.1	$>10^4$	46

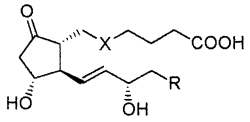
Using membrane fractions of CHO cells expressing the prostanoid receptors, the mouse (m) EP-receptor or human (h) IP-receptor, K_i values were determined by competitive binding assay, which was performed according to the method of Kiriyama et al. with some modifications.[13] With regard to the subtype-receptor agonist activity, EC_{50} values were determined based on the effects of the test compounds on the increase in the intracellular c-AMP production.

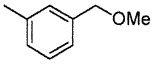
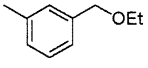
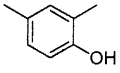
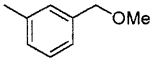
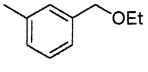
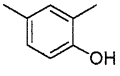
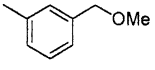
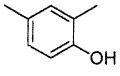
5-thiaPGE$_1$ **3** with potent agonistic activity. However, 6-thiaPGE$_1$ **53** and 4-thiaPGE$_1$ **54** demonstrated EP3 selectivity with marked reduction of the EP4-receptor agonist activity. In addition, 3-thiaPGE$_1$ **55** also showed EP3-receptor selectivity with moderate EP4-receptor agonist activity. Thus, the EP4-receptor selectivity and the potent agonist activity of the thiaPGEs were acceptable only in 7-thiaPGE$_1$ and 5-thiaPGE$_1$. Due to its chemical stability, 5-thiaPGE$_1$ **3** was selected as one of the chemical leads for further modification.

Introduction of the optimized ω chain moieties in the discovery process of 3,7-dithiaPGE$_1$ analogues **4** and **5** into the corresponding position of PGE$_1$ and PGE$_2$ afforded the compounds listed in Table 2. 16-(*m*-Methoxymethyl)phenylPGE$_2$ **22a** and 16-(*m*-ethoxymethyl)-phenylPGE$_2$ **22b** demonstrated the higher EP4-receptor selectivity than PGE$_2$ retaining the agonist activity, while 16-(3-methyl-4-hydroxy)phenylPGE$_2$ **22c** showed decreased agonist activity although it exhibited potent EP4-receptor selectivity. In the EP4-receptor selectivity, introduction of the optimized ω chain moieties into PGE$_1$ (**26a**–**c**) was superior to that of PGE$_2$ (**22a**–**c**). The agonist activities of the 16-(*m*-alkoxymethyl)phenyl-PGE$_1$ derivatives were nearly the same as those of the corresponding PGE$_2$ derivatives. With regard to 16-(4-hydroxy-3-methyl)phenyl derivatives, the EC$_{50}$ value of **26c** was nearly 3-fold more potent than that of **22c**. SAR of the ω chain moieties found in the process of optimization of 3,7-dithiaPGEs[3] was thought to be acceptable in these cases.

We focused our attention on this EP4-receptor-selective structural information. Based on the results shown in Tables 1 and 2, we planned compounds **33a** and **33c** with hybrid structures. These compounds showed excellent profiles as EP4-receptor-selective agonists in both subtype selectivity and agonist activity. The easily enolizable structure 'α-alkylthiacyclopentanone' of the 3,7-dithiaPGE$_1$ skeleton was successfully replaced by

Table 2. Biological evaluation of 16-phenyl-ω-tetranorPGE$_1$ analogues



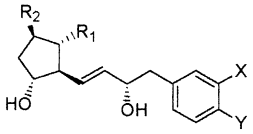
Compound	X	R	Binding K_i (nM)					EC_{50} (nM)
			mEP1	mEP2	mEP3	mEP4	hlP	mEP4
1 (PGE$_2$)	–CH=CH–		6	22	5.0	3.1	$>10^4$	3.6
22a	–CH=CH–		$>10^4$	480	290	5.0	$>10^4$	28
22b	–CH=CH–		$>10^4$	700	540	10	$>10^4$	12
22c	–CH=CH–		$>10^4$	$>10^4$	$>10^4$	20	$>10^4$	190
2 (PGE$_1$)	–CH$_2$–CH$_2$–		22	41	5.0	3.3	$>10^4$	2.5
26a	–CH$_2$–CH$_2$–		$>10^4$	1400	820	6.0	$>10^4$	24
26b	–CH$_2$–CH$_2$–		$>10^4$	760	3600	6.9	$>10^4$	18
26c	–CH$_2$–CH$_2$–		$>10^4$	3500	$>10^4$	3.0	$>10^4$	61
33a	–CH$_2$–S–		$>10^4$	620	56	0.7	$>10^4$	1.6
33c	–CH$_2$–S–		$>10^4$	7400	2900	4.9	$>10^4$	20

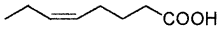
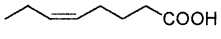
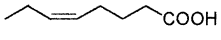
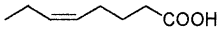
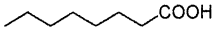
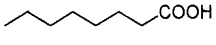
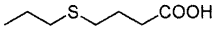
the more chemically stable 5-thiaPGE$_1$ skeleton with potent agonist activity and the selectivity. The chemical instability of 5-thiaPGEs generated from the dehydration reaction of the partial structure 'β-hydroxycyclopentanone' of the PGE skeleton was partially improved by converting **33a** to the corresponding methyl ester **32a**, because of the reduced acidity.

PGE derivatives, which contain a β-hydroxyketone moiety, show self-degradation starting from conversion to the corresponding PGA derivatives. On the other hand, it is possible to avoid these degradation pathways in PGF derivatives. The results of biological evaluation of 9β-haloPGF derivatives **39, 41** and **46** are shown in Table 3. Replacement of the *n*-amyl moiety of 9β-chloroPGF$_2$[12] with the optimized ω chain moieties afforded **39a**, **39b** and **39c**. These compounds exhibited potent EP4-receptor affinity and agonist activity, while their subtype-selectivity to EP2- and EP3-receptors remained to be improved. The corresponding PGF$_1$ analogues **46a** and **46c** exhibited potent EP4-receptor affinity and more improved subtype selectivity, while their agonist activities were much less potent than those of **39a** and **39c**, respectively. 9β-Fluoro analogue **41a** showed biological properties similar to those of the corresponding 9-chloro analogue **39a**. However, the 9β-chloro-5-thiaPGF$_1$ analogue was too unstable to carry out precise biological evaluation. Presumably, this might have been due to intramolecular nucleophilic attack by the sulfur atom at position 5 as described previously in the preceding communication.[14] 9β-Fluoro-5-thiaPGF$_1$ **51a** was stably prepared and biologically evaluated. This compound demonstrated good subtype selectivity regarding EP4-receptor affinity, while the agonist activity was not improved compared with that of **46a**. Thus, all the 9-haloPGF$_2$ and PGF$_1$ derivatives **39**, **41**, **46** and **51** tended to show EP4-receptor selectivity in their binding assay, and the agonist activities of PGF$_2$ derivatives **39** and **41** tended to be more potent than those of PGF$_1$ derivatives **46** and **51**.

The biological activities of EP4-receptor agonists were investigated in vivo using compound **32a**. Intravenous infusion of the methyl ester **32a** (10–300 ng/kg/min), which was metabolically hydrolyzed to the active form **33a**, suppressed the increased production of plasma TNF-α level and augmented the plasma IL-10 level in LPS-induced rats.[15] Subcutaneous administration of **32a** (10–100 μg/kg) also exhibited excellent efficacy in the rat hepatitis model induced by *Propionibacterium acnes*/LPS or GalN/LPS in a dose-dependent manner.[14] As such, the EP4-receptor was estimated to mediate various cytoprotective activities of PGE$_2$ by regulation of cytokine production. More detailed biological analyses of the EP4-receptor-selective ligands are currently in progress in our laboratory and the details of these studies will be reported in due course.

Table 3. Biological evaluation of 9β-haloPGF analogues



Compound	R1	R2	X	Y	Binding K_i (nM)					EC_{50} (nM)
					mEP1	mEP2	mEP3	mEP4	hIP	mEP4
39a		Cl	CH_2OMe	H	980	12	92	0.5	$>10^4$	3.3
39b		Cl	CH_2OEt	H	7000	24	44	1.5	$>10^4$	1.9
39c		Cl	Me	OH	3100	290	2200	7.7	$>10^4$	44
41a		F	CH_2OMe	H	1700	58	94	3.4	$>10^4$	14
46a		Cl	CH_2OMe	H	5400	370	740	2.7	$>10^4$	160
46c		Cl	Me	OH	2100	1400	$>10^4$	48	$>10^4$	730
51a		F	CH_2OMe	H	$>10^4$	3100	1500	32	$>10^4$	270

Summary

To identify EP4-receptor selective agonists applicable to clinical studies, we continued chemical modification of those reported previously. Among the compounds tested, 5-thiaPG analogues **33a**, **33c** and 9-β-haloPG analogue **39a** were investigated. The methyl ester **32a** of **33a** was selected as a clinical candidate because of its improved chemical stability. Compound **32a**, which metabolically produces **33a**, did not show uterine contractile activity at the therapeutic dose. These observations indicated that **32a** showed subtype-selectivity in vivo.

Experimental

General procedures

Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned structures. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on a Varian Gemini-200, VXR-200s or Mercury300 spectrometer using deuterated chloroform ($CDCl_3$) or deuterated methanol (CD_3OD) as the solvent. Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL JMS-DX303HF spectrometer. Atmospheric pressure chemical ionization (APCI) was obtained on a Hitachi M1200H spectrometer. Infrared spectra (IR) were measured on a Perkin-Elmer FT-IR 1760X spectrometer. Melting points and results of elemental analyses were uncorrected. Column chromatography was carried out on silica gel [Merck silica gel 60 (0.063∼0.200 mm), Wako gel C200 or Fuji Silysia BW235]. Thin layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, silica gel 60 F_{254}). The following abbreviations for solvents and reagents are used: tetrahydrofuran (THF), ethyl acetate (EtOAc), dimethylformamide (DMF), dichloromethane (CH_2Cl_2), methanol (MeOH), acetic acid (AcOH), *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O), pyridinium poly(hydrogen fluoride) [$(HF)_n$·py, Aldrich], porcine liver esterase (PLE).

Preparation of optically active vinyl iodide 18a–c

2-(*S*)-Hydroxy-3-(3-methoxymethyl)phenylpropan-1-ol trityl ether 8a. Magnesium turnings (5.83 g, 0.240 mol) were dried and heated in vacuo with vigorous stirring for 1 h under Ar. Then, anhydrous THF (100 mL) and 10 drops of 1,2-dibromoethane were added. To this mixture was added dropwise a solution of **6a** (40.2 g, 0.200 mol) in THF (100 mL) in 45 min at room temperature (exothermic). The resulting dark yellow solution was stirred for an additional 30 min and transferred to a suspension of copper (I) iodide (3.24 g, 17 mmol) in THF (100 mL) at 0 °C. The resulting gray suspension was stirred for an additional 30 min and then treated with **7** (53.8 g, 0.170 mol) in THF (100 mL). The reaction mixture was stirred for 20 min and then poured into saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation to give **8a** as a yellow oil (95.8 g, >100%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.5–7.1 (m, 19H), 4.40 (s, 2H), 4.1–3.9 (m, 1H), 3.37 (s, 3H), 3.3–3.1 (m, 2H), 2.9–2.7 (m, 2H), 2.23 (brd, 1H).

2-(*S*)-Hydroxy-3-(3-ethoxymethyl)phenylpropan-1-ol trityl ether 8b. 95% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.01 (m, 19H), 4.44 (s, 2H), 4.05–3.93 (m, 1H), 3.51 (q, J = 7.2 Hz, 2H), 3.20 (dd, J = 9.3, 4.5 Hz, 1H), 3.13 (dd, J = 9.3, 6.3 Hz, 1H), 2.81 (dd, J = 13.8, 5.5 Hz, 1H), 2.74 (dd, J = 13.8, 7.5 Hz, 1H), 2.21 (d, J = 4.5 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H).

2-(*S*)-Hydroxy-3-(4-tetrahydropyranyloxy-3-methyl)phenylpropan-1-ol trityl ether 8c. 100% yield; ^{1}H NMR (200 MHz, CDCl3): δ 7.5–7.2 (m, 16H), 7.0–6.85 (m, 2H), 5.4–5.35 (m, 1H), 4.0–3.8 (m, 2H), 3.65–3.5 (m, 1H), 3.2–3.1 (m, 2H), 2.8–2.6 (m, 2H), 2.21 (s, 3H), 2.25–2.15 (m, 1H), 2.1–1.5 (m, 6H).

2-(*S*)-Hydroxy-3-(3-methoxymethyl)phenylpropan-1-ol 9a. A solution of **8a** (95.7 g) in THF (40 mL) was diluted with AcOH (200 mL) and H_2O (40 mL). After stirring for 3 h at 65 °C, 160 mL of water was added at that temperature. The reaction mixture was cooled to room temperature and the precipitates were removed by filtration and washed with AcOH–H_2O (50–50 mL). The filtrate was concentrated and the contained water was removed by azeotropic evaporation with toluene to give **9a** as a pale brown oil (46.9 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.10 (m, 4H), 4.43 (s, 2H), 4.05–3.90 (m, 1H), 3.71 (dd, J = 11, 3 Hz, 1H), 3.52 (dd, J = 11. 7 Hz, 1H), 3.41 (s, 3H), 2.8–2.7 (m, 2H), 2.2–1.5 (br, 2H).

2-(*S*)-Hydroxy-3-(3-ethoxymethyl)phenylpropan-1-ol 9b. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36–7.10 (m, 4H), 4.48 (s, 2H), 4.00–3.89 (m, 1H), 3.69 (dd, J = 11.4, 3.3 Hz, 1H), 3.56 (q, J = 7.2 Hz, 2H), 3.51 (dd, J = 11.4, 6.9 Hz, 1H), 2.80 (dd, J = 13.9, 6.0 Hz, 1H), 2.74 (dd, J = 13.9, 7.8 Hz, 1H), 2.36–1.90 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H).

2-(*S*)-Hydroxy-3-(4-hydroxy-3-methyl)phenylpropan-1-ol 9c. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.98–6.82 (m, 2H), 6.70 (d, J = 7 Hz, 1H), 4.10–3.92 (m, 1H), 3.67–3.40 (m, 2H), 3.0–2.7 (br), 2.75–2.61 (m, 2H), 2.21 (s, 3H).

2-(*S*)-1-Acetoxy-3-(3-methoxymethyl)phenylpropane-2-ol 10a. To a pre-cooled (−78 °C) solution of **9a** (46.9 g) and 2,4,6-collidine (45 mL, 0.34 mol) in CH_2Cl_2 (300 mL) was slowly added a solution of acetyl chloride (17 mL, 0.238 mol) in CH_2Cl_2 (30 mL) over 20 min under Ar. After stirring for an additional 20 min, the reaction was quenched with MeOH (5 mL, 0.12 mol) and then poured into 1 N HCl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with water, and dried over $MgSO_4$. The solvent was removed by evaporation to half of the volume. The resulting solution of **10a** was used for the next reaction. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.1 (m, 4H), 4.43 (s, 2H), 4.25–3.95 (m, 3H), 3.41 (s, 3H), 2.9–2.8 (m, 2H), 2.12 (s, 3H).

2-(*S*)-1-Acetoxy-3-(3-ethoxymethyl)phenylpropane-2-ol 10b. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44–7.02 (m, 4H), 4.48 (s, 2H), 4.17 (dd, J = 10.8, 2.7 Hz, 1H), 4.14–4.06 (m, 1H), 4.01 (dd, J = 10.8, 6.6 Hz, 1H), 3.55 (q, J = 6.9 Hz, 2H), 2.89–2.74 (m, 2H), 2.10 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H).

2-(*S*)-1-Acetoxy-3-(4-hydroxy-3-methyl)phenylpropane-2-ol 10c. Compound **10c,** which was prepared from **54c**, was used for the next reaction without purification.

1-Acetoxy-3-(3-methoxymethyl)phenyl-2-(*S*)-tetrahydropyranyloxypropane 11a. To a stirred solution of **10a** in CH_2Cl_2 (ca. 200 mL) was successively added 3,4-dihydropyran (24 mL, 0.26 mol) and *p*-TsOHH_2O (0.32 g, 1.7 mmol) at room temperature under Ar. After stirring for 30 min, the reaction mixture was treated with Et_3N (0.47 mL, 3.4 mmol) and then evaporated. The residue was dissolved in EtOAc (100 mL) and hexane (200 mL) and washed with 1 N HCl, water, saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). The solvent was removed by evaporation to give **11a** as a pale yellow oil (57.6 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 4.85–4.8 and 4.45–4.0 (m, 1H), 4.43 (s, 2H), 4.25–3.85 and 3.5–3.2 (m, 5H), 3.39 (s, 3H), 3.05–2.8 (m, 2H), 2.10 and 2.08 (s, 3H), 1.9–1.4 (m, 6H).

1-Acetoxy-3-(3-ethoxymethyl)phenyl-2-(*S*)-tetrahydropyranyloxypropane 11b. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.08 (m, 4H), 4.86–4.40 (m, 1H), 4.47 (s, 2H), 4.28–3.24 (m, 7H), 3.04–2.78 (m, 2H), 2.08 (s, 3H), 1.94–1.30 (m, 6H), 1.24 (t, J = 7.0 Hz, 3H).

1-Acetoxy-3-(4-tetrahydropyranyloxy-3-methyl)phenyl-2-(*S*)-tetrahydropyranyloxypropane 11c. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.07–6.93 (m, 3H), 5.41–5.35 (m, 1H), 4.88–4.82 and 4.51–4.44 (m, 1H), 4.24–3.81 (m, 4H), 3.67–3.28 (m, 3H), 2.96–2.71 (m, 2H), 2.23 (s, 3H), 2.08 and 2.05 (s, 3H), 1.96–1.40 (m, 12H).

2-(*S*)-Tetrahydropyranyloxy-3-(3-methoxymethyl)phenylpropan-1-ol 12a. A solution of **11a** (57.6 g) in 200 mL of MeOH was treated with 2 N NaOH (100 mL) at room temperature. After stirring for 30 min, the reaction mixture was concentrated to half of the volume and the resulting suspension was diluted with water (200 mL). The mixture was extracted with diethyl ether repeatedly and the combined organic layer was washed with brine and dried ($MgSO_4$). Concentration and purification by column chromatography on silica gel (EtOAc/hexane, 1/3∼1/1) provided **12a** as a yellow oil (43.6 g, 92% from **8a**). R_f 0.51, 0.41 (diastereomeric mixture, EtOAc/hexane, 2/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 4.85–4.8 and 4.25–4.2 (m, 1H), 4.42 (s, 2H), 4.05–3.4 (m, 5H), 3.38 (s, 3H), 3.06 (dd, J = 14, 6 Hz, 1H), 2.85 (dd, J = 14, 8 Hz, 1H), 2.8–2.7 and 2.15–2.05 (m, 1H), 1.9–1.4 (m, 6H).

2-(*S*)-Tetrahydropyranyloxy-3-(3-ethoxymethyl)phenylpropan-1-ol 12b. 51% yield from **8b**; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.09 (m, 4H), 4.85–4.18 (m, 1H), 4.47 (s, 2H), 4.04–3.36 (m, 7H), 3.09–2.65 (m, 2H), 1.88–1.36 (m, 7H), 1.24 (t, J = 7.0 Hz, 3H).

2-(*S*)-Tetrahydropyranyloxy-3-(4-tetrahydropyranyloxy-3-methyl)phenylpropan-1-ol 12c. 51% yield from **8c**; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05–6.9 (m, 3H), 5.4–5.35 (m, 1H), 4.85–4.8 and 4.3–4.2 (m, 1H), 4.05–3.4 (m, 7H), 3.0–2.5 (m, 2H), 2.23 (s, 3H), 2.1–1.4 (m, 12H).

2-(*S*)-Tetrahydropyranyloxy-3-(3-methoxymethyl)phenylpropan-1-al 13a. To a stirred solution of oxalyl chloride (21.1 mL, 0.242 mol) in CH_2Cl_2 (250 mL) was slowly added a solution of dry DMSO (34.3 mL, 0.484 mol) in CH_2Cl_2 (50 mL) at −70 °C in 10 min. The resulting solution was stirred for an additional 15 min at that temperature and a solution of **12a** (34.2 g, 0.121 mol) in CH_2Cl_2 (100 mL) was added. After stirring for 30 min, the reaction mixture was treated with Et_3N (101 mL, 0.726 mol) and the resulting suspension was allowed to warm to −30 °C in 15 min. The reaction was quenched with H_2O (50 mL) and then poured into ice-cold 0.5 N HCl. The mixture was extracted with diethyl ether and the organic layer was washed with 1 N HCl, water and brine, and dried ($MgSO_4$). Removal of the solvent by evaporatoion gave **13a** as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.75–9.00 (m, 1H), 7.30–7.10 (m, 4H), 4.80–4.75 and 4.35–4.30 (m, 1H), 4.43 (s, 2H), 4.45–4.30 and 4.10–4.00 (m, 1H), 3.95–3.90 and 3.50–3.40 (m, 1H), 3.40 (s, 3H), 3.30–2.80 (m, 3H), 1.90–1.30 (m, 6H).

2-(*S*)-Tetrahydropyranyloxy-3-(3-ethoxymethyl)phenylpropan-1-al 13b. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.71 (d, J = 2.0 Hz, 1/2H), 9.69 (d, J = 1.4 Hz, 1/2H), 7.35–7.01 (m, 4H), 4.80–4.74 (m, 1/2H), 4.44–4.27 (m, 1H), 4.48 (s, 2H), 4.18–3.80 (m, 3/2H), 3.62–2.78 (m, 5H), 1.92–1.30 (m, 6H), 1.24 (t, J = 6.8 Hz, 3H).

2-(*S*)-Tetrahydropyranyloxy-3-(4-tetrahydropyranyloxy-3-methyl)phenylpropan-1-al 13c. Compound **13c**, which was prepared from **12c**, was used for the next reaction without further purification.

1,1-Dibromo-3-(*S*)-tetrahydropyranyloxy-4-(3-methoxymethyl)phenyl-1-butene 14a. To a stirred solution of carbontetrabromide (120 g, 0.363 mol) in CH_2Cl_2 (400 mL) was added a solution of triphenylphosphine (190 g, 0.726 mol) in CH_2Cl_2 (320 mL) at −30 °C in 20 min. The resulting orange solution was cooled to −40 °C and then a cooled solution (−40 °C) of **13a** and Et_3N (17.3 mL, 0.124 mol) in CH_2Cl_2 (120 mL) was added dropwise in 10 min. After stirring for 15 min, triethylamine (34.6 mL, 0.248 mol) and MeOH (29.4 mL, 0.726 mol) were successively added. The resulting orange solution was diluted with 500 mL of ether and the precipitates were removed by filtration. The filtrate was concentrated to half of the volume and the precipitates were removed by filtration again. The filtrate was concentrated and purified by short column chromatography on silica gel (EtOAc/hexane, 1/4) to give **14a** as a pale yellow oil (49.2 g, 93% yield from **12a**). ^{1}H NMR (200 MHz, CDCl3) δ 7.35–7.12 (m, 4H), 6.54 and 6.37 (d, J = 7 Hz, 1H), 4.70–4.59 (m, 1H), 4.50–4.38 (m, 3H), 3.90–3.70 and 3.55–3.40 (m, 1H), 3.39 (s, 3H), 3.38–3.10 and 3.03–2.83 (m, 3H), 1.82–1.30 (m, 6H).

1,1-Dibromo-3-(*S*)-tetrahydropyranyloxy-4-(3-ethoxymethyl)phenyl-1-butene 14b. 63% yield from **12b**; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.10 (m, 4H), 6.53 and 6.34 (d, J = 8.4 Hz, 1H), 4.70–4.54 (m, 1H), 4.49 (s, 2H), 4.46–4.36 (m, 1H), 3.90–3.40 (m, 3H), 3.36–3.10 (m, 1H), 3.02–2.76 (m, 2H), 1.88–1.30 (m, 6H), 1.24 (t, J = 7.0 Hz, 3H).

1,1-Dibromo-3-(*S*)-tetrahydropyranyloxy-4-(4-tetrahydropyranyloxy-3-methyl)phenyl-1-butene 14c. 79% yield from **12c**; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.1–6.95 (m, 3H), 6.52 and 6.34 (d, J = 9 Hz, 1H), 5.4–5.35 (m, 1H), 4.7–4.65 and 4.45–4.4 (m, 1H), 4.65–4.5 and 4.45–4.3 (m, 1H), 4.0–3.2 (m, 4H), 2.9–2.7 (m, 2H), 2.23 (s, 3H), 2.1–1.3 (m, 12H).

3-(*S*)-Tetrahydropyranyloxy-4-(3-methoxymethyl)phenyl-1-butyne 15a To a stirred solution of **14a** (49.2 g, 0.113 mol) in THF (340 mL) was added dropwise *n*-butyllithium (1.54 M in hexane, 161 mL, 0.249 mmol) in 30 min at −70 °C. The reaction mixture was stirred for an additional 15 min and then poured into aqueous NH_4Cl. The mixture was extracted with EtOAc twice and the organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed by evaporation to give **15a** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.14 (m, 4H), 5.03–4.98 and 4.60–4.42 (m, 2H), 4.44 (s, 2H), 4.06–3.95 and 3.55–3.48 (m, 1H), 3.37 (s, 3H), 3.39–3.11 (m, 1H), 3.10–2.97 (m, 2H), 2.45 and 2.38 (d, J = 2.1 Hz, 1H), 1.89–1.25 (m, 6H).

3-(*S*)-Tetrahydropyranyloxy-4-(3-ethoxymethyl)phenyl-1-butyne 15b. 77% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.13 (m, 4H), 5.05–4.40 (m, 4H), 4.10–3.44 (m, 3H), 3.40–2.98 (m, 3H), 2.45 and 2.38 (d, J = 2.0 Hz, 1H), 1.95–1.30 (m, 6H), 1.24 (t, J = 7.0 Hz, 3H).

3-(*S*)-Tetrahydropyranyloxy-4-(4-tetrahydropyranyloxy-3-methyl)phenyl-1-butyne 15c. Compound **15c,** which was prepared from **14c**, was used for the next reaction without further purification.

3-(*S*)-Hydroxy-4-(3-methoxymethyl)phenyl-1-butyne 16a. A solution of **15a** in MeOH (50 mL) was treated with *p*-TsOH•H_2O (1.07 g, 5.63 mmol) at room temperature. After stirring for 30 min, the reaction mixture was diluted with EtOAc, washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography on silica gel (EtOAc/hexane, 1/4) provided **16a** as a pale yellow oil (12.4 g, 58% yield from **14a**). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.1 (m, 4H), 6.52 (d, J = 8 Hz, 1H), 4.65–4.5 (m, 1H), 4.45 (s, 2H), 3.40 (s, 3H), 2.94 (dd, J = 14, 4 Hz, 1H), 2.81 (dd, J = 14, 8 Hz, 1H), 1.90 (brd).

3-(*S*)-Hydroxy-4-(3-ethoxymethyl)phenyl-1-butyne 16b. 89% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.15 (m, 4H), 4.59 (td, J = 6.4, 2.0 Hz, 1H), 4.50 (s, 2H), 3.55 (q, J = 7.0 Hz, 2H), 3.14–2.92 (m, 2H), 2.48 (d, J = 2.0 Hz, 1H), 2.02–1.50 (br, 1H), 1.24 (t, J = 7.0 Hz, 3H).

3-(*S*)-Hydroxy-4-(4-hydroxy-3-methyl)phenyl-1-butyne 16c. 85% yield from **14c**; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05–6.95 (m, 2H), 6.73 (d, J = 8 Hz, 1H), 4.73 (s, 1H), 4.53 (dq, J = 6, 2 Hz, 1H), 2.92 (dd, J = 6, 2 Hz, 2H), 2.49 (d, J = 2 Hz, 1H), 2.24 (s, 3H), 1.90 (d, J = 6 Hz, 1H).

3-(*S*)-*t*-Butyldimethylsilyloxy-4-(3-methoxymethyl)phenyl-1-butyne 17a. To a stirred solution of **16a** (12.2 g, 64.0 mmol) and imidazole (6.53 g, 96.0 mmol) in DMF (70 mL) was added *t*-butyldimethylsilyl chloride (11.6 g, 77.1 mmol) in several portions at room temperature. After stirring overnight, the resulting solution was poured into ice-cooled water and the mixture was extracted with EtOAc–hexane (1:4) twice. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. Concentration and purification by column chromatography (EtOAc/hexane, 1/40) afforded **17a** as a colorless oil (21.0 g, 97%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 4.5–4.45 (m, 1H), 4.44 (s, 2H), 3.37 (s, 3H), 3.0–2.95 (m, 2H), 2.41 (d, J = 2 Hz, 1H), 0.83 (s, 9H), −0.02 (s, 3H), −0.08 (s, 3H).

3-(*S*)-*t*-Butyldimethylsilyloxy-4-(3-ethoxymethyl)phenyl-1-butyne 17b. 89% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.11 (m, 4H), 4.54–4.40 (m, 3H), 3.52 (q, J = 7.0 Hz, 2H), 3.07–2.86 (m, 2H), 2.40 (d, J = 2.2 Hz, 1H), 1.23 (t, J = 7.0 Hz, 3H), 0.82 (s, 9H), −0.02 (s, 3H), −0.07 (s, 3H).

3-(*S*)-*t*-Butyldimethylsilyloxy-4-(4-*t*-butyldimethylsilyloxy-3-methyl)phenyl-1-butyne 17c. 100% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.98 (d, J = 2 Hz, 1H), 6.90 (dd, J = 8, 2 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 4.39 (ddd, J = 8, 6, 2 Hz, 1H), 2.9–2.8 (m, 2H), 2.41 (d, J = 2 Hz, 1H), 2.17 (s, 3H), 1.01 (s, 9H), 0.83 (s, 9H), 0.18 (s, 6H), −0.04 (s, 3H), −0.09 (s, 3H).

3-(*S*)-*t*-Butyldimethylsilyloxy-1-iodo-4-(3-methoxymethyl)-phenyl-1-butene 18a. To a stirred suspension of Cp_2ZrClH (19.9 g, 77.2 mmol) in THF (40 mL) was added **17a** (20.0 g, 62.1 mmol) in THF (80 mL) at room temperature under Ar and the reaction mixture was stirred for 45 min. Then, the reaction mixture was cooled to 0 °C and treated with a solution of iodine (15.5 g, 61.0 mmol) in THF (80 mL). After stirring for 15 min, the brown solution was diluted with hexane (300 mL) and the resulting suspension was passed through a short column using 10% EtOAc/hexane as an eluent. The combined fraction was concentrated and the residue was purified by flash column chromatography on silica gel (EtOAc/hexane, 1/40) to give **18a** as a pale red oil (21.86 g, 80%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.05 (m, 4H), 6.56 (dd, J = 15, 5 Hz, 1H), 6.19 (dd, J = 15, 1 Hz, 1H), 4.43 (s, 2H), 4.3–4.15 (m, 1H), 3.38 (s, 3H), 2.8–2.7 (m, 2H), 0.83 (s, 9H), −0.08 (s, 3H), −0.11 (s, 3H).

3-(*S*)-*t*-Butyldimethylsilyloxy-1-iodo-4-(3-ethoxymethyl)-phenyl-1-butene 18b. 58% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.02 (m, 4H), 6.55 (dd, J = 14.4, 5.7 Hz, 1H), 6.18 (dd, J = 14.4 Hz, 1.0 Hz, 1H), 4.48 (s, 2H), 4.30–4.16 (m, 1H), 3.52 (q, J = 7.0 Hz, 2H), 2.84–2.66 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H), 0.82 (s, 9H), −0.08 (s, 3H), −0.21 (s, 3H).

3-(*S*)-*t*-Butyldimethylsilyloxy-1-iodo-4-(4-*t*-butyldimethylsilyloxy-3-methyl)phenyl-1-butene 18c. 93% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.91 (d, $J=2$ Hz, 1H), 6.83 (dd, $J=8$, 2 Hz, 1H), 6.67 (d, $J=8$ Hz, 1H), 6.56 (dd, $J=14$, 6 Hz, 1H), 6.17 (dd, $J=14$, 2 Hz, 1H), 4.2–4.1 (m, 1H), 2.65–2.6 (m, 2H), 2.17 (s, 3H), 1.01 (s, 9H), 0.83 (s, 9H), 0.18 (s, 6H),−0.10 (s, 3H),−0.22 (s, 3H).

Synthesis of PGE and PGF derivatives

16-(3-Methoxymethyl)phenyl-ω-tetranorPGE$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 20a. To a stirred solution of 3-(*S*)-*t*-butyldimethylsilyloxy-1-iodo-4-(3-methoxymethyl)phenyl-1-butene **18a** (1.27 g, 2.93 mmol) in freshly distilled dry diethyl ether (12 mL) was slowly added *t*-butyllithium (1.64M in pentane, 3.58 mL, 5.87 mmol) at −70 °C under Ar and stirring was continued for 1 h at that temperature. To the resulting suspension was slowly added lithium 2-thienylcyanocuprate (0.25 M in THF, 12.7 mL, 3.16 mmol) and the yellow suspension was stirred for 15 min and then a solution of 4-(*R*)-*t*-butyldimethylsilyloxy-2-(6-carbomethoxy-2-hexenyl)-2-cyclopentenone **19** (800 mg, 2.26 mmol) in THF (4 mL) was added dropwise in 5 min. The resulting yellowish mixture was stirred for a further 15 min at −70 °C and then warmed to −20 °C over 50 min. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was vigorously stirred for 30 min without cooling. The two layers were separated and the aqueous layer was extracted with hexane. The combined organic layer was washed with aqueous NH_3/NH_4Cl (1/9), water and brine, and dried over $MgSO_4$. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/20 to 1/10) to afford **20a** as a yellow oil (1.34 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$,) δ 7.30–7.01 (m, 4H), 5.71–5.20 (m, 4H), 4.42 (s, 2H), 4.29 (m, 1H), 4.04 (m, 1H), 3.66 (s, 3H), 3.38 (s, 3H), 2.94–1.92 (m, 12H), 1.74–1.60 (m, 2H), 0.89 (s, 9H), 0.83 (s, 9H), 0.07, 0.05, −0.12 and −0.29 (s, 3H).

16-(3-Ethoxymethyl)phenyl-ω-tetranorPGE$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 20b. 79% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.05 (m, 4H), 5.64 (dd, $J=15.2$, 4.5 Hz, 1H), 5.53 (dd, $J=15.2$, 7.6 Hz, 1H), 5.45–5.25 (m, 2H), 4.47 (s, 2H), 4.32–4.22 (m, 1H), 4.09–3.98 (m, 1H), 3.65 (s, 3H), 3.52 (q, $J=6.9$ Hz, 2H), 2.82–1.94 (m, 12H), 1.74–1.60 (m, 2H), 1.23 (t, $J=6.9$ Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.06, 0.05, −0.11 and −0.29 (each s, 3H).

16-(4-*t*-butyldimethylsilyloxy-3-methyl)phenyl-ω-tetranorPGE$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 20c. 79% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, $J=2$ Hz, 1H), 6.83 (dd, $J=8$, 2 Hz, 1H), 6.66 (d, $J=8$ Hz, 1H), 5.63 (dd, $J=16$, 4 Hz, 1H), 5.52 (dd, $J=16$, 8 Hz, 1H), 5.45–5.25 (m, 2H), 4.25–4.15 (m, 1H), 4.04 (q, $J=7$ Hz, 1H), 3.66 (s, 3H), 2.7–1.95 (m, 12H), 2.17 (s, 3H), 1.7–1.6 (m, 2H), 1.01 and 0.89 (s, 9H) 0.84 (s, 9H), 0.18 (s, 6H), 0.07, 0.06, −0.11 and −0.27 (each s, 3H).

16-(3-Methoxymethyl)phenyl-ω-tetranorPGE$_2$ methyl ester 21a. A solution of **20a** (1.34 g, 2.0 mmol) and pyridine (1 mL) in acetonitrile (15 mL) was cooled in an ice-bath and treated with $(HF)_n$·py (Aldrich, 2 mL). The reaction mixture was stirred for 90 min without cooling. Then, the solution was slowly poured into a biphasic solution of EtOAc and saturated aqueous $NaHCO_3$ with stirring. The two layers were separated and the aqueous layer was extracted with EtOAc. The combined EtOAc layer was washed with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography (EtOAc/hexane, 2/1 ∼ EtOAc/MeOH, 20/1) to give **21a** as pale yellow oil (740 mg, 84%). IR (neat) 3402, 2923, 1740, 1439, 1368, 1159, 1090, 1032, 972, 704 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3–7.1 (m, 4H), 5.71 (dd, $J=15$, 6 Hz, 1H), 5.50 (dd, $J=15$, 8 Hz, 1H), 5.5–5.2 (m, 2H), 4.42 (s, 2H), 4.45–4.3 (m, 1H), 4.0–3.85 (m, 1H), 3.68 (s, 3H), 3.41 (s, 3H), 2.95–2.8 (m, 2H), 2.68 (dd, $J=18$, 7 Hz, 1H), 2.5–2.0 (m, 11H), 1.8–1.6 (m, 2H); MS (APCI) m/z: 413 $(M-H_2O+H)^+$.

16-(3-Ethoxymethyl)phenyl-ω-tetranorPGE$_2$ methyl ester 21b. 73% yield in two steps; IR (neat) 3409, 2867, 1741, 1439, 1354, 1245, 1159, 1090, 1031, 972 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3–7.1 (m, 4H), 5.72 (dd, $J=15$, 6 Hz, 1H), 5.51 (dd, $J=15$, 8 Hz, 1H), 5.5–5.2 (m, 2H), 4.47 (s, 2H), 4.42 (q, $J=6$ Hz, 1H), 4.0–3.85 (m, 1H), 3.66 (s, 3H), 3.58 (q, $J=7$ Hz, 2H), 3.15–3.0 (m, 1H), 2.95–2.8 (m, 2H), 2.69 (dd, $J=19$, 7 Hz, 1H), 2.45–2.2 (m, 10H), 1.8–1.6 (m, 2H), 1.26 (t, $J=7$ Hz, 3H); MS (APCI) m/z: 427 $(M-H_2O+H)^+$.

16-(4-Hydroxy-3-methyl)phenyl-ω-tetranorPGE$_2$ methyl ester 21c. 80% yield; IR (neat) 3399, 2927, 1736, 1510, 1438, 1266, 1158, 1079, 818, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.88 (d, $J=8$ Hz, 1H), 6.69 (d, $J=8$ Hz, 1H), 5.70 (dd, $J=16$, 6 Hz, 1H), 5.52 (dd, $J=16$, 8 Hz, 1H), 5.45–5.2 (m, 2H), 5.25 (s, 1H), 4.4–4.25 (m, 1H), 4.1–3.9 (m, 1H), 3.68 (s, 3H), 2.85–2.6 (m, 4H), 2.5–2.2 (m, 6H), 2.22 (s, 3H), 2.2–2.0 (m, 3H), 1.8–1.6 (m, 3H); MS (APCI) m/z: 399 $(M-H_2O+H)^+$.

16-(3-Methoxymethyl)phenyl-ω-tetranorPGE$_2$ 22a. A heterogeneous mixture of **21a** (460 mg, 1.1 mmol) and porcine liver esterase (PLE) (Sigma, 20000U, 0.1 mL) in EtOH (1 mL) and phosphate buffer (pH 7.4, 5 mL) was vigorously stirred for 3 h at room temperature. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ and the mixture was extracted with EtOAc twice. The combined organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 50/1–20/1) to afford **22a** as a pale yellow oil (400 mg, 87%). IR (neat) 3392, 2931, 1739, 1447, 1243, 1194, 1159, 1087, 1032, 972, 915, 793, 733, 705cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 5.71 (dd, $J=15$, 6 Hz, 1H), 5.52 (dd, $J=15$, 8 Hz, 1H), 5.45–5.3 (m, 2H), 4.42 (s, 2H), 4.5–4.35 (m, 1H), 4.0–3.85 (m, 1H), 4.2–3.3 (br), 3.42 (s, 3H), 2.9–2.8 (m, 2H), 2.68 (dd, $J=18$, 7 Hz, 1H), 2.45–2.0 (m, 9H), 1.8–1.6 (m, 2H); MS (FAB) m/z: 417 $(M+H)^+$; HRMS (MALDI-TOF) calcd for $C_{24}H_{32}O_6+Na^+$: 439.2097; found: 439.2112.

16-(3-Ethoxymethyl)phenyl-ω-tetranorPGE$_2$ 22b. 83% yield; IR (neat) 3392, 2931, 1737, 1047, 1243, 1158, 1085, 972, 704 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3–7.1 (m, 4H), 5.72 (dd, J=15, 6 Hz, 1H), 5.52 (dd, J=15, 8 Hz, 1H), 5.45–5.3 (m, 2H), 4.47 (s, 2H), 4.5–4.4 (m, 1H), 3.92 (q, J=8 Hz, 1H), 3.59 (q, J=7 Hz, 2H), 3.9–3.1 (br), 2.9–2.8 (m, 2H), 2.69 (dd, J=18, 7 Hz, 1H), 2.4–2.0 (m, 9H), 1.8–1.6 (m, 2H), 1.25 (t, J=7 Hz, 3H); MS (APCI) m/z: 429 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{25}H_{34}O_6+Na^+$: 453.2253; found: 453.2237.

16-(4-Hydroxy-3-methyl)phenyl-ω-tetranorPGE$_2$ 22c. 97% yield; IR (neat) 3377, 3014, 2926, 1733, 1510, 1423, 1348, 1265, 1215, 1157, 1077, 1032, 972, 819, 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.89 (s, 1H), 6.83 (d, J=8 Hz, 1H), 6.63 (d, J=8 Hz, 1H), 5.61 (dd, J=15, 6 Hz, 1H), 5.48 (dd, J=15, 8 Hz, 1H), 5.4–5.2 (m, 2H), 4.23 (q, J=6 Hz, 1H), 4.00 (q, J=8 Hz, 1H), 2.78 (dd, J=18, 6 Hz, 1H), 2.7–2.5 (m, 2H), 2.4–2.2 (m, 4H), 2.14(s, 3H), 2.2–2.0 (m, 5H), 1.8–1.6 (m, 2H); MS (APCI) 401 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{23}H_{30}O_6+Na^+$: 425.1940; found: 425.1914.

16-(3-Methoxymethyl)phenyl-ω-tetranorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 24a. To a stirred solution of 3-(*S*)-*t*-butyldimethylsilyloxy-1-iode-4-(3-methoxymethyl)phenyl-1-butene **18a** (1.27 g, 2.93 mmol) in freshly distilled dry diethyl ether (12 mL) was slowly added *t*-butyllithium (1.64 M in pentane, 3.58 mL, 5.87 mmol) at −70 °C under Ar and the stirring was continued for 1 h at that temperature. To the resulting suspension was slowly added lithium 2-thienylcyanocuprate (0.25 M in THF, 12.7 mL, 3.16 mmol) and the yellow suspension was stirred for 15 min and then a solution of 4-(*R*)-*t*-butyldimethylsilyloxy-2-(6-carbomethoxyhexyl)-2-cyclopentenone **23** (800 mg, 2.26 mmol) in THF (5 mL) was added dropwise in 5 min. The resulting yellowish mixture was stirred for a further 15 min at −70 °C and then warmed to −20 °C over 50 min. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was vigorously stirred for 30 min without cooling. The two layers were separated and the aqueous layer was extracted with hexane. The combined organic layer was washed with aqueous NH_3/NH_4Cl (1/9), water and brine, and dried over $MgSO_4$. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/20–1/10) to afford **24a** as a yellow oil (1.05 g, 70%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.02 (m, 4H), 5.64 (dd, J=15, 4.2 Hz, 1H), 5.54 (dd, J=15, 6.9 Hz, 1H), 4.42 (s, 2H), 4.27 (m, 1H), 4.03 (m, 1H), 3.65 (s, 3H), 3.38 (s, 3H), 2.8–2.65 (m, 2H), 2.59 (ddd, J=18, 7.0, 1.1 Hz, 1H), 2.44 (m, 1H), 2.28 (t, J=7.5 Hz, 2H), 2.16 (dd, J=18, 8.0 Hz, 1H), 1.90 (m, 1H), 1.68–1.12 (m, 10H).0.88 (s, 9H), 0.83 (s, 9H), 0.07, 0.05, −0.13 and −0.29 (each s, 3H).

16-(3-Ethoxymethyl)phenyl-ω-tetranorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 24b. 40% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.01 (m, 4H), 5.65 (dd, J=15, 4.4 Hz, 1H), 5.53 (dd, J=15, 7.0 Hz, 1H), 4.47 (s, 2H), 4.34–4.22 (m, 1H), 4.09–3.95 (m, 1H), 3.65 (s, 3H), 3.52 (q, J=7.0 Hz, 2H), 2.82–1.80 (m, 8H), 1.70–1.08 (m, 13H), 0.88 (s, 9H), 0.82 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), −0.13 (s, 3H), −0.28 (s, 3H).

16-(4-*t*-butyldimethylsilyloxy-3-methyl)phenyl-ω-tetranorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 24c. 61% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J=2 Hz, 1H), 6.83 (dd, J=8, 2 Hz, 1H), 6.66 (d, J=8 Hz, 1H), 5.7–5.55 (m, 2H), 4.25–4.15 (m, 1H), 4.1–3.95 (m, 1H), 3.66 (s, 3H), 2.7–2.0 (m, 10H), 2.0–1.8 (m, 1H), 1.7–1.2 (m, 10H), 1.01, 0.89 and 0.84 (each s, 9H), 0.18 (s, 6H), 0.08, 0.06, −0.12 and −0.26 (each s, 3H).

16-(3-Methoxymethyl)phenyl-ω-tetranorPGE$_1$ methyl ester 25a. A solution of **24a** (1.01 g, 1.53 mmol) and pyridine (2 mL) in acetonitrile (20 mL) was cooled in an ice-bath and treated with $(HF)_n$·py (Aldrich, 4 mL). The reaction mixture was stirred for 120 min without cooling. Then, the solution was slowly poured into a biphasic solution of EtOAc and saturated aqueous $NaHCO_3$ with stirring. The two layers were separated and the aqueous layer was extracted with EtOAc. The combined EtOAc layer was washed with 1N HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography (EtOAc/hexane, 2/1 ∼ EtOAc/MeOH, 20/1) to give **25a** as pale yellow oil (535 mg, 81%). IR (neat) 3392, 2931, 1732, 1436, 1160, 1094, 1031, 971, 888, 792, 757, 704 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (m, 1H), 7.23–7.10 (m, 3H), 5.72 (dd, J=15, 6.2 Hz, 1H), 5.51 (dd, J=15, 8.9 Hz, 1H), 4.48–4.35 (m, 3H), 3.93 (m, 1H), 3.65 (s, 3H), 3.41 (s, 3H), 2.90 (dd, J=14, 5.3 Hz, 1H), 2.82 (dd, J=14, 7.1 Hz, 1H), 2.68 (dd, J=18, 7.5 Hz, 1H), 2.32 (m, 1H), 2.29 (t, J=7.4 Hz, 2H), 2.20 (dd, J=18, 9.8 Hz, 1H), 1.96 (m, 1H), 1.66–1.16 (m, 10H); MS (APCI) m/z: 415 $(M-H_2O+H)^+$.

16-(3-Ethoxymethyl)phenyl-ω-tetranorPGE$_1$ methyl ester 25b. 60% yield; IR (neat) 3392, 2932, 2858, 1740, 1440, 1373, 1354, 1245, 1159, 1098, 1029, 972, 791, 756, 704 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (m, 1H), 7.23–7.10 (m, 3H), 5.72 (dd, J=15, 6.2 Hz, 1H), 5.51 (dd, J=15, 8.9 Hz, 1H), 4.48–4.35 (m, 3H), 3.93 (m, 1H), 3.65 (s, 3H), 3.41 (s, 3H), 2.90 (dd, J=14, 5.3 Hz, 1H), 2.82 (dd, J=14, 7.1 Hz, 1H), 2.68 (dd, J=18, 7.5 Hz, 1H), 2.32 (m, 1H), 2.29 (t, J=7.4 Hz, 2H), 2.20 (dd, J=18, 9.8 Hz, 1H), 1.96 (m, 1H), 1.66–1.16 (m, 10H); MS (APCI) m/z: 429 $(M-H_2O+H)^+$.

16-(4-Hydroxy-3-methyl)phenyl-ω-tetranorPGE$_1$ methyl ester 25c. 84% yield; IR (neat) 3400, 2931, 1737, 1510, 1438, 1266, 1209, 1119, 818 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.0–6.8 (m, 2H), 6.71 (d, J=8 Hz, 1H), 5.70 (dd, J=16, 6 Hz, 1H), 5.52 (s, 1H), 5.49 (dd, J=16, 8 Hz, 1H), 4.4–4.3 (m, 1H), 4.1–3.9 (m, 1H), 3.78 (s, 3H), 2.8–2.6 (m, 4H), 2.4–2.1 (m, 8H), 2.0–1.85 (m, 1H), 1.7–1.2 (m, 10H); MS (APCI) m/z: 401 $(M-H_2O+H)^+$.

16-(3-Methoxymethyl)phenyl-ω-tetranorPGE$_1$ 26a. A heterogeneous mixture of **25a** (320 mg, 0.74 mmol) and porcine liver esterase (PLE) (Sigma, 20000U, 0.2 mL) in

EtOH (5 mL) and phosphate buffer (pH 7.4, 25 mL) was vigorously stirred for 3 h at room temperature. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ and the mixture was extracted with EtOAc twice. The combined organic layer was dried (Na_2SO_4) and concentrated and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50/1–20/1) to afford **26a** as a colorless oil (275 mg, 90%). IR (neat) 3391, 2928, 1732, 1715, 1455, 1385, 1159, 1085, 971, 793, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31–7.09 (m, 4H), 5.73 (dd, $J=15$, 6.2 Hz, 1H), 5.52 (dd, $J=15$, 8.9 Hz, 1H), 4.49–4.34 (m, 3H), 3.93 (m, 1H), 3.50 (br, 3H), 3.41 (s, 3H), 2.88 (dd, $J=14$, 5.4 Hz, 1H), 2.82 (dd, $J=14$, 7.4 Hz, 1H), 2.68 (ddd, $J=18$, 7.4, 0.9 Hz, 1H), 2.32 (m, 1H), 2.31 (t, $J=7.4$ Hz, 2H), 2.20 (dd, $J=18$, 9.8 Hz, 1H), 1.96 (m, 1H), 1.68–1.18 (m, 10H); MS (FAB) m/z: 419 $(M+H)^+$; HRMS (MALDI-TOF) calcd for $C_{24}H_{34}O_6+Na^+$: 441.2253; found: 441.2238.

16-(3-Ethoxymethyl)phenyl-ω-tetranorPGE$_1$ 26b. 87% yield; IR (neat) 3600–3200, 2931, 2858, 1733, 1446, 1411, 1353, 1243, 1159, 1084, 972, 791, 757, 705, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.06 (m, 4H), 5.70 (dd, $J=15.3$, 6.6 Hz, 1H), 5.48 (dd, $J=15.3$, 8.4 Hz, 1H), 5.30–4.60 (br), 4.46 (s, 2H), 4.42–4.28 (m, 1H), 4.00–3.82 (m, 1H), 3.57 (q, $J=7.0$ Hz, 2H), 2.94–2.58 (m, 3H), 2.42–2.08 (m, 4H), 2.04–1.86 (m, 1H), 1.72–1.14 (1m, 3H); MS (FAB) m/z: 419 $(M+H)^+$; HRMS (MALDI-TOF) calcd for $C_{25}H_{36}O_6+Na^+$: 455.2410; found: 455.2407.

16-(4-Hydroxy-3-methyl)phenyl-ω-tetranorPGE$_1$ 26c. 95% yield; IR (neat) 3370, 2931, 1732, 1514, 1265, 1119, 972, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.9–6.75 (m, 2H), 6.62 (d, $J=8$ Hz, 1H), 5.60 (dd, $J=16$, 6 Hz, 1H), 5.46 (dd, $J=16$, 8 Hz, 1H), 4.3–4.15 (m, 1H), 4.05–3.9 (m, 1H), 2.79 (dd, $J=14$, 6 Hz, 1H), 2.7–2.5 (m, 2H), 2.4–2.2 (m, 1H), 2.28 (t, $J=7$ Hz, 2H), 2.14 (s, 3H), 2.2–1.9 (m, 2H), 1.7–1.2 (m, 10H); MS (APCI) 403 $(M-H)^-$.

7-Hydroxy-16-(3-methoxymethyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 29a. To a stirred solution of 3-(*S*)-*t*-butyldimethylsilyloxy-1-iodo-4-(3-methoxymethyl)phenyl-1-butene **18a** (200 mg, 0.46 mmol) in freshly distilled dry diethyl ether (2 mL) was slowly added *t*-butyllithium (1.64 M in pentane, 0.56 mL, 0.92 mmol) at −70 °C under Ar and stirring was continued for 1 h at that temperature. To the resulting suspension was slowly added lithium 2-thienylcyanocuprate (0.25 M in THF, 2.0 mL, 0.51 mmol). The yellow suspension was stirred for 15 min and then a solution of 4-(*R*)-*t*-butyldimethylsilyloxy-2-cyclopentenone **27** (97 mg, 0.46 mmol) in THF (0.5 mL) was added dropwise in 3 min. The resulting yellowish mixture was stirred for an additional 30 min at −70 °C, then 6-methoxycarbonyl-3-thia-hexanal **28** (90 mg, 0.51 mmol) was added. After stirring for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was vigorously stirred for 30 min without cooling and then extracted with diethyl ether repeatedly. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/4) to give **29a** as a pale brown oil (174 mg, 55%). ^1H NMR (200 MHz, $CDCl_3$) δ 7.3–7.05 (m, 4H), 5.68 (dd, $J=16$, 5 Hz, 1H), 5.50 (dd, $J=16$, 8 Hz, 1H), 4.43 (s, 2H), 4.35–4.2 (m, 1H), 4.15–4.0 (m, 1H), 3.75–3.65 (m, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.9–2.7 (m, 5H), 2.65–2.5 (m, 3H), 2.43 (t, $J=7$ Hz, 2H), 2.35–2.2 (m, 2H), 2.0–1.8 (m, 2H), 0.90 (s, 9H), 0.85 (s, 9H), 0.10, 0.08, −0.10 and −0.22 (each s, 3H).

7-Hydroxy-16-(4-*t*-butyldimethylsilyloxy-3-methyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 29c. 79% yield; ^1H NMR (200 MHz, $CDCl_3$) δ 6.92 (d, $J=2$ Hz, 1H), 6.83 (dd, $J=8$, 2 Hz, 1H), 6.67 (d, $J=8$ Hz, 1H), 5.69 (dd, $J=15$, 4 Hz, 1H), 5.55 (dd, $J=15$, 7 Hz, 1H), 4.25–4.0 (m, 1H), 4.08 (q, $J=6$ Hz, 1H), 3.85–3.8 (m, 1H), 3.68 (s, 3H), 3.36 (d, $J=3$ Hz, 1H), 2.89 (dd, $J=14$, 8 Hz, 1H), 2.85–2.7 (m, 2H), 2.7–2.5 (m, 5H), 2.43 (t, $J=7$ Hz, 2H), 2.35–2.2 (m, 2H), 2.16 (s, 3H), 1.9–1.85 (m, 2H), 1.01, 0.89 and 0.83 (each s, 9H), 0.18 (s, 6H), 0.10, 0.08, −0.11 and −0.23 (each s, 3H).

7,8-Δ-16-(3-Methoxymethyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 30a. To a stirred solution of **29a** (170 mg, 0.24 mmol) and DMAP (195 mg, 1.6 mmol) in CH_2Cl_2 (2 mL) was added methanesulfonyl chloride (0.061 mL, 0.72 mmol) at 0 °C and the resulting suspension was stirred at that temperature for 3 h. Then the reaction mixture was poured into water and extracted with hexane repeatedly. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/6) to afford **30a** as a pale yellow oil (127 mg, 78%). ^1H NMR (200 MHz, $CDCl_3$) δ 7.3–7.0 (m, 4H), 6.8–6.65 (m, 1H), 5.6–5.45 (m, 2H), 4.42 (s, 2H), 4.3–4.2 (m, 1H), 4.15–4.1 (m, 1H), 3.67 (s, 3H), 3.45–3.4 (m, 1H), 3.39 (s, 3H), 3.2–3.05 (m, 2H), 2.8–2.7 (m, 2H), 2.6–2.2 (m, 6H), 2.0–1.8 (m, 2H), 0.85 (s, 9H), 0.83 (s, 9H), 0.08, 0.06, −0.12 and −0.20 (each s, 3H).

7,8-Δ-16-(4-*t*-Butyldimethylsilyloxy-3-methyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 30c. 81% yield; ^1H NMR (200 MHz, $CDCl_3$) δ 6.92–6.62 (m, 3H), 5.53–5.46 (m, 1H), 4.27–4.11 (m, 2H), 3.68 (s, 3H), 3.44–3.38 (m, 1H), 3.26–3.01 (m, 2H), 2.75–2.20 (m, 8H), 2.18 (s, 3H), 1.97–1.80 (m, 2H), 1.02 (s, 9H), 0.94–0.81 (m, 18H), 0.21 (s, 6H), 0.07, 0.02, −0.12 and −0.19 (each s, 3H).

16-(3-Methoxymethyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31a. A mixture of **30a** (125 mg, 0.18 mmol) and tributyltinhydride (1 mL) was stirred at 100 °C in the presence of a catalytic amount of *t*-butylperoxide. After stirring for 2 h, a catalytic amount of azobisisobutyronitrile (AIBN, ca. 10 mg) was added. The reaction mixture was stirred for an additional 30 min, cooled and purified by column chromatography (hexane to EtOAc/hexane, 1/10) to give **31a** as a pale yellow oil (33 mg, 27%).

16-(4-*t*-butyldimethylsilyloxy-3-methyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) **31c**. 47%

16-(3-Methoxymethyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester 32a. A solution of **31a** (33 mg, 0.049 mmol) and pyridine (0.1 mL) in acetonitrile (1.5 mL) was cooled in an ice-bath and treated with $(HF)_n$·py (Aldrich, 0.2 mL). The reaction mixture was stirred for 90 min without cooling. Then, the solution was slowly poured into a heterogenious mixture of EtOAc and saturated aqueous $NaHCO_3$ under stirring. The two layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/1 to EtOAc) to give **32a** as a yellow oil (16 mg, 73%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.1 (m, 4H), 5.75 (dd, J = 16, 6 Hz, 1H), 5.52 (dd, J = 16, 8 Hz, 1H), 4.42 (s, 2H), 4.45–4.35 (m, 1H), 4.0–3.85 (m, 1H), 3.67 (s, 3H), 3.42 (s, 3H), 3.3–3.2 (m, 1H), 3.0–2.1 (m, 13H), 2.0–1.8 (m, 3H), 1.8–1.6 (m, 1H).

16-(4-Hydroxy-3-methyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester 32c. 76% yield; IR (neat) 3400, 2921, 1736, 1510, 1439, 1266, 1120, 1078, 820, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.87 (d, J = 8 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 5.71 (dd, J = 15, 7 Hz, 1H), 5.62 (s, 1H), 5.50 (dd, J = 15, 8 Hz, 1H), 4.4–4.2 (m, 1H), 4.1–3.9 (m, 1H), 3.68 (s, 3H), 3.35–3.3 (br, 1H), 2.8–2.6 (m, 3H), 2.6–2.4 (m, 7H), 2.4–2.1 (m, 3H), 2.22 (s, 3H), 2.0–1.8 (m, 3H), 1.7–1.5 (m, 1H); MS (APCI) m/z: 435 $(M-H)^-$.

16-(3-Methoxymethyl)phenyl-ω-tetranor-5-thiaPGE$_1$ 33a. A heterogeneous mixture of **32a** (16 mg, 0.035 mmol) and porcine liver esterase (PLE) (Sigma, 20000U, 0.1 mL) in DMSO (1 mL) and phosphate buffer (Ph 7.4, 1 mL) was stirred for 1 h at room temperature. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ and the mixture was extracted with EtOAc twice. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography on silica gel (EtOAc/hexane/AcOH, 50/50/1 to EtOAc/AcOH, 100/1) to afford **33a** as a pale yellow oil (13 mg, 85%). IR (neat) 3392, 2923, 1737, 1447, 1158, 1087, 972, 913, 792, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.1 (m, 4H), 5.76 (dd, J = 15, 6 Hz, 1H), 5.53 (dd, J = 15, 8 Hz, 1H), 5.2–4.4 (br, 3H), 4.43 (s, 2H), 4.5–4.4 (m, 1H), 3.94 (q, J = 8 Hz, 1H), 3.42 (s, 3H), 3.0–2.15 (m, 13H), 2.0–1.8 (m, 2H), 1.8–1.6 (m, 1H); MS (APCI) m/z: 435 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{23}H_{32}O_6S + Na^+$: 459.1817; found: 459.1850.

16-(4-Hydroxy-3-methyl)phenyl-ω-tetranor-5-thiaPGE$_1$ 33c. 92% yield; IR (neat) 3369, 2923, 1733, 1423, 1264, 1120, 1077, 973, 754 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD): δ 6.89 (s, 1H), 6.82 (d, J = 8 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 5.64 (dd, J = 15, 7 Hz, 1H), 5.48 (dd, J = 15, 8 Hz, 1H), 4.22 (q, J = 7 Hz, 1H), 3.99 (q, J = 8 Hz, 1H), 2.9–2.1 (m, 13H), 2.15 (s, 3H), 1.9–1.6 (m, 3H); MS (APCI) m/z: 421 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{22}H_{30}O_6S + Na^+$: 445.1661; found: 445.1672.

16-(3-Methoxymethyl)phenyl-ω-tetranorPGF$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 34a. To a stirred solution of **20a** (186 mg, 0.27 mmol) in anhydrous THF (3 mL) was slowly added lithium tri-*s*-butylborohydride (1.0 M solution in THF, 0.32 mL, 0.32 mmol) at −70 °C. After stirring for 1 h, 1 N HCl was added. The reaction mixture was allowed to warm to room temperature and then extracted with EtOAc. The organic layer was washed with water and brine, and dried (Na_2SO_4). After removal of solvent by evaporation, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/6–1/4) to give **34a** as a yellow oil (77 mg, 42%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29–7.04 (m, 4H), 5.57–5.26 (m, 4H), 4.42 (s, 2H), 4.22 (m, 1H), 4.08 (m, 1H), 3.99 (m, 1H), 3.65 (s, 3H), 3.37 (s, 3H), 2.74 (d, J = 6.4 Hz, 2H) 2.40–2.01 (m, 8H), 1.88–1.56 (m, 4H), 0.88 (s, 9H), 0.82 (s, 9H), 0.05 (s, 6H), −0.12 (s, 3H), −0.24 (s, 3H).

16-(3-Ethoxymethyl)phenyl-ω-tetranorPGF$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 34b. 58% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29–7.02 (m, 4H), 5.50 (dd, J = 15.4, 5.2 Hz, 1H), 5.45–5.26 (m, 3H), 4.46 (s, 2H), 4.30–3.94 (m, 3H), 3.64 (s, 3H), 3.52 (q, J = 7.0 Hz, 2H), 2.73 (d, J = 6.6 Hz, 2H) 2.41–1.32 (m, 13H), 1.23 (t, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.81 (s, 9H), 0.04 (s, 6H), −0.12 (s, 3H), −0.23 (s, 3H).

16-(4-*t*-butyldimethylsilyloxy-3-methyl)phenyl-ω-tetranorPGF$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 34c. 61% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.92 (d, J = 2 Hz, 1H), 6.84 (dd, J = 8, 2 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 5.55–5.3 (m, 4H), 4.16 (q, J = 7 Hz, 1H), 4.1–4.05 (m, 1H), 4.1–3.95 (m, 1H), 3.67 (s, 3H), 2.7–2.6 (m, 3H), 2.32 (t, J = 7 Hz, 2H), 2.4–2.2 (m, 2H), 2.17 (s, 3H), 2.2–2.1 (m, 3H), 1.85–1.8 (m, 2H), 1.75–1.65 (m, 2H), 1.5–1.4 (m, 1H), 1.01 and 0.89 (s, 9H), 0.83 (s, 9H), 0.18 (s, 6H), 0.07, 0.06, −0.11 and −0.20 (each s, 3H).

16-(3-Methoxymethyl)phenyl-9-*O*-tosyl-ω-tetranorPGF$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 35a. A solution of **34a** (95 mg, 0.14 mmol) and *p*-toluenesulfonyl chloride (0.53 g, 2.8 mmol) in anhydrous pyridine (1.5 mL) was stirred at room temperature overnight. Then, the mixture was poured into ice-cooled 1 N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4) and evaporated to give **35a** as crude product, which was used for the next reaction without further purification. Compound **35b** and **35c** were prepared from **34a** and **34c**, respectively according to the same procedure as described above.

9β-Chloro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 36a. A mixture of crude **35a** and tetrabutylammonium chloride (0.39 g, 1.4 mmol) in anhydrous toluene (6 mL) was stirred at 55 °C for 1 h. The

reaction mixture was cooled to room temperature and then poured into water. The mixture was extracted with EtOAc and the organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed by evaporation to give **36a**, which was used for the next reaction without further purification. Compounds **36b** and **36c** were prepared from **35a** and **35c**, respectively, according to the procedure described above.

9β-Chloro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_2$ methyl ester 38a. A solution of crude **36a** and *p*-TsOH·H_2O (10 mg) in MeOH (2 mL) was stirred at room temperature for 1 h. Then, the reaction mixture was poured into water and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by short column chromatography to remove polar product. The combined fractions were concentrated and further purified by passage through a Lobar column (Merck, sizeA, *i*PrOH/toluene, 1/20) to give **38a** as a colorless oil (38 mg, 58% in three steps). IR (neat) 3400, 2930, 1737, 1438, 1364, 1247, 1195, 1159, 1094, 1031, 970, 791, 754, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33–7.08 (m, 4H), 5.60 (dd, $J=15$, 6.2 Hz, 1H), 5.42 (m, 3H), 4.42 (s, 2H), 4.33 (m, 1H), 3.99 (m, 2H), 3.67 (s, 3H), 3.40 (s, 3H), 2.9–2.7 (m, 2H), 2.32 (t, $J=7.5$ Hz, 2H), 2.33–1.83 (m, 8H), 1.8–1.6 (m, 2H); MS (APCI) *m*/*z*: 435 and 433 $(M-H_2O+H)^+$.

9β-Chloro-9-deoxy-16-(3-ethoxymethyl)phenyl-ω-tetranorPGF$_2$ methyl ester 38b. 48% yield in three steps; IR (neat) 3600–3200, 2931, 1738, 1440, 1373, 1249, 1158, 1098, 1029, 971, 790, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.05 (m, 4H), 5.57 (dd, $J=15$, 6.5 Hz, 1H), 5.51–5.26 (m, 3H), 4.45 (s, 2H), 4.36–4.22 (m, 1H), 4.06–3.90 (m, 2H), 3.66 (s, 3H), 3.55 (q, $J=7.0$ Hz, 2H), 3.02–2.68 (m, 4H), 2.38–1.82 (m, 10H), 1.78–1.58 (m, 2H), 1.24 (t, $J=7.0$ Hz, 3H); MS (APCI) *m*/*z*: 449 and 447 $(M-H_2O+H)^+$.

9β-Chloro-9-deoxy-16-(4-hydroxy-3-methyl)phenyl-ω-tetranorPGF$_2$ methyl ester 38c. 65% in three steps; IR (neat) 3369, 2927, 1715, 1436, 1266, 1211, 1120, 1031, 972, 819, 734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.88 (d, $J=8$ Hz, 1H), 6.69 (d, $J=8$ Hz, 1H), 5.60 (dd, $J=15$, 6 Hz, 1H), 5.55–5.35 (m, 3H), 5.19 (s, 1H), 4.4–4.2 (m, 1H), 4.15–3.9 (m, 2H), 3.69 (s, 3H), 2.74 (d, $J=7$ Hz, 1H), 2.34 (t, $J=7$ Hz, 2H), 2.22 (s, 3H), 2.1–1.8 (m, 9H), 1.8–1.6 (m, 3H); MS (APCI) *m*/*z*: 437 and 435 $(M-H)^-$.

9β-Chloro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_2$ 39a. To a stirred solution of **38a** (28 mg, 0.059 mmol) in MeOH (2 mL) was added 2 N NaOH (1 mL) at room temperature. The reaction mixture was stirred for 1 h, then poured into 1 N HCl and extracted with EtOAc twice. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 20/1) to afford **39a** as a colorless oil (24 mg, 89%). IR (neat) 3368, 2930, 1708, 1447, 1408, 1242, 1194, 1159, 1089, 1031, 971, 912, 791, 734, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.33–7.08 (m, 4H), 5.60 (dd, $J=15$, 5.8 Hz, 1H), 5.45 (m, 3H), 4.7–4.3 (br), 4.43 (s, 2H), 4.37 (m, 1H), 3.99 (m, 2H), 3.40 (s, 3H), 2.84 (d, $J=6.6$ Hz, 2H), 2.34 (t, $J=7.0$ Hz, 2H), 2.28–1.84 (m, 8H), 1.8–1.6 (m, 2H); MS (APCI) *m*/*z*: 437 and 435 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{24}H_{33}ClO_5+Na^+$: 459.1914; found: 459.1869.

9β-Chloro-9-deoxy-16-(3-ethoxymethyl)phenyl-ω-tetranorPGF$_2$ 39b. 91% yield; IR (neat) 3600–3200, 2975, 2931, 1708, 1445, 1408, 1353, 1244, 1159, 1094, 1029, 971, 911, 790, 734, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33–7.06 (m, 4H), 6.00–5.20 (m, 7H), 4.46 (s, 2H), 4.40–4.26 (m, 1H), 4.07–3.90 (m, 2H), 3.56 (q, $J=7.0$ Hz, 2H), 2.81 (d, $J=6.2$ Hz, 2H), 2.40–1.80 (m, 10H), 1.78–1.58 (m, 2H), 1.24 (t, $J=7.0$ Hz, 3H); MS (APCI) *m*/*z*: 451 and 449 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{25}H_{35}ClO_5+Na^+$: 473.2071; found: 473.2071.

9β-Chloro-9-deoxy-16-(4-hydroxy-3-methyl)phenyl-ω-tetranorPGF$_2$ 39c. 99% yield; IR (neat) 3369, 2931, 1714, 1510, 1435, 1264, 1043, 972, 819 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.81 (d, $J=8$ Hz, 1H), 6.62 (d, $J=8$ Hz, 1H), 5.50 (dd, $J=15$, 6 Hz, 1H), 5.5–5.3 (m, 3H), 4.18 (q, $J=6$ Hz, 1H), 4.05–3.9 (m, 2H), 2.77 (dd, $J=14$, 6 Hz, 1H), 2.57 (dd, $J=14$, 8 Hz, 1H), 2.29 (t, $J=7$ Hz, 2H), 2.12 (s, 3H), 2.2–1.9 (m, 7H), 1.9–1.7 (m, 1H), 1.75–1.55 (m, 2H); MS (APCI) *m*/*z*: 423 and 421 $(M-H)^-$.

9β-Fluoro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_2$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 37a. A mixture of crude **35a** (prepared from 77 mg of **34a**) and tetrabutylammonium fluoride (prepared by concentration of 1.0 M THF solution, 0.30 g, 1.16 mmol) in anhydrous toluene (6 mL) was stirred at 55 °C for 1 h. The reaction mixture was cooled to room temperature, then poured into water and extracted with EtOAc. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed by evaporation to give **37a**, which was used for the next reaction without further purification.

9β-Fluoro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_2$ methyl ester 40a. A solution of crude **37a** and *p*-TsOH·H_2O (10 mg) in MeOH (2 mL) was stirred at room temperature for 1 h. Then, the reaction mixture was poured into water and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by short column chromatography on silica gel to remove polar product. The combined fractions were concentrated and further purified by passage through a Lobar column (Merck, sizeA, *i*PrOH/toluene, 1/20) to give **40a** as an yellow oil (11 mg, 22% in three steps). IR (neat) 3392, 2931, 1738, 1438, 1364, 1315, 1195, 1159, 1096, 1031, 971, 792, 754, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33–7.08 (m, 4H), 5.61 (dd, $J=15$, 6.2 Hz, 1H), 5.47 (dd, $J=15$, 7.4 Hz, 1H), 5.53–5.29 (m,

2H), 4.72 (m, 1H), 4.42 (s, 2H), 4.33 (m, 1H), 3.98 (m, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.86 (dd, $J=14$, 5.6 Hz, 1H), 2.79 (dd, $J=14$, 7.0 Hz, 1H), 2.32 (t, $J=7.3$ Hz, 2H), 2.39–1.58 (m, 10H); MS (APCI) m/z: 417 $(M-H_2O+H)^+$.

9β-Fluoro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_2$ 41a. To a stirred solution of **40a** (7.0 mg, 0.016 mmol) in MeOH (1 mL) was added 2 N NaOH (0.5 mL) at room temperature. The reaction mixture was stirred for 1 h, then poured into 1 N HCl and extracted with EtOAc twice. The organic layer was washed with water and brine, then dried (Na_2SO_4). The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 20/1) to afford **41a** as a colorless oil (6.5 mg, 96%). IR (neat) 3368, 2930, 1708, 1448, 1382, 1241, 1194, 1159, 1093, 1030, 971, 922, 792, 704 cm^{-1}; ^{1}H NMR (200 MHz, CDCl3) δ 7.36–7.08 (m, 4H), 5.63 (dd, $J=15$, 5.8 Hz, 1H), 5.57–5.31 (m, 3H), 4.77 (m, 1H), 4.43 (s, 2H), 4.42 (m, 1H), 4.4–3.9 (br), 3.98 (m, 1H), 3.41 (s, 3H), 3.0–2.8 (m, 2H), 2.40–1.54 (m, 12H); MS (APCI) m/z: 419 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{24}H_{33}FO_5+Na^+$: 443.2210; found: 443.2232.

16-(3-Methoxymethyl)phenyl-ω-tetranorPGF$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 42a. To a stirred solution of **24a** (278 mg, 0.42 mmol) in anhydrous THF (8 mL) was slowly added L-selectride (1.0M solution in THF, 0.46 mL, 0.46 mmol) at −70 °C. After stirring for 1 h, to this solution was added 30% H_2O_2. The reaction mixture was allowed to warm to room temperature, then poured into 1 N HCl and extracted with EtOAc. The organic layer was washed with water and brine, and dried (Na_2SO_4). After removal of the solvent by evaporation, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/10 to 1/4) to give **42a** as a colorless oil (174 mg, 62%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.03 (m, 4H), 5.48 (dd, $J=15.4$, 5.6 Hz, 1H), 5.34 (dd, $J=15.4$, 8.6 Hz, 1H), 4.42 (s, 2H), 4.29–3.94 (m, 3H), 3.65 (s, 3H), 3.37 (s, 3H), 2.73 (d, $J=6.6$ Hz, 2H) 2.29 (t, $J=7.5$ Hz, 2H), 2.24–2.12 (m, 1H), 1.86–1.10 (m, 14H), 0.86 (s, 9H), 0.81 (s, 9H), 0.04 (s, 6H), −0.12 (s, 3H), −0.23 (s, 3H).

16-(4-*t*-butyldimethylsilyloxy-3-methyl)phenyl-ω-tetranorPGF$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 42c. 74% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, $J=2$ Hz, 1H), 6.82 (dd, $J=8$, 2 Hz, 1H), 6.65 (d, $J=8$ Hz, 1H), 5.48 (dd, $J=15$, 6 Hz, 1H), 5.35 (dd, $J=15$, 9 Hz, 1H), 4.2–4.1 (m, 2H), 4.0–3.95 (m, 1H), 3.65 (s, 3H), 2.8–2.7 (m, 3H), 2.63 (d, $J=7$ Hz, 2H), 2.29 (t, $J=7$ Hz, 2H), 2.25–2.15 (m, 1H), 2.17 (s, 3H), 1.85–1.8 (m, 2H), 1.7–1.5 (m, 5H), 1.5–1.2 (m, 8H), 1.01 and 0.87 and 0.83 (each s, 9H), 0.18 (s, 6H), 0.05 (s, 6H), −0.13 and −0.21 (each s, 3H).

16-(3-Methoxymethyl)phenyl-9-*O*-tosyl-ω-tetranorPGF$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 43a. A solution of **42a** (174 mg, 0.26 mmol) and *p*-toluenesulfonyl chloride (1.0 g, 5.2 mmol) in anhydrous pyridine (3 mL) was stirred at room temperature for 21 h. Then, the mixture was poured into ice-cooled 1 N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4) and evaporated to give **43a** as a crude product, which was used for the next reaction without further purification. Compound **43c** was prepared from **42c** according to the procedure described above.

9β-Chloro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 44a. A mixture of crude **43a** and tetrabutylammonium chloride (0.39 g, 1.4 mmol) in anhydrous toluene (6 mL) was stirred at 55 °C for 1 h. The reaction mixture was cooled to room temperature, then poured into water and extracted with EtOAc. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed by evaporation to give **44a**, which was used to the next reaction without further purification. Compound **44c** was prepared from **43c** according to the procedure described above.

9β-Chloro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_1$ methyl ester 45a. A solution of crude **44a** and *p*-TsOH·H_2O (10 mg) in MeOH (3 mL) was stirred at room temperature for 1 h. Then, the reaction mixture was poured into water and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by short-column chromatography to remove polar products. The combined fractions were concentrated and further purified by passage through a Lobar column (Merck, sizeA, *i*PrOH/toluene, 1/20) to give **45a** as a yellow oil (56 mg, 46% in three steps). IR (neat) 3600–3200, 2928, 2857, 1738, 1440, 1363, 1261, 1196, 1099, 1032, 971, 791, 704 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.06 (m, 4H), 5.56 (dd, $J=15.0$, 6.2 Hz, 1H), 5.42 (dd, $J=15.0$, 7.6 Hz), 4.41 (s, 2H), 4.36–4.20 (m, 1H), 4.08–3.90 (m, 2H), 3.65 (s, 3H), 3.63–3.42 (br, 1H), 3.39 (s, 3H), 2.92–2.68 (m, 3H), 2.30 (t, $J=7.5$ Hz, 2H), 2.25–1.20 (m, 14H); MS (APCI) m/z; 435 $(M-H_2O+H)^+$.

9β-Chloro-9-deoxy-16-(4-hydroxy-3-methyl)phenyl-ω-tetranorPGF$_1$ methyl ester 45c. 58% in three steps; IR (neat) 3392, 2929, 2857, 1718, 1510, 1439, 1266, 1210, 1120, 1034, 972, 911, 818, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, $J=2$ Hz, 1H), 6.86 (dd, $J=8$, 2 Hz, 1H), 6.70 (d, $J=8$ Hz, 1H), 5.59 (dd, $J=15$, 6 Hz, 1H), 5.47 (dd, $J=15$, 8 Hz, 1H), 5.38 (s, 1H), 4.35–4.25 (m, 1H), 4.1–4.0 (m, 1H), 4.0–3.9 (m, 1H), 3.68 (s, 3H), 2.76 (d, $J=7$ Hz, 2H), 2.34 (t, $J=7$ Hz, 2H), 2.23 (s, 3H), 2.3–2.1 (m, 2H), 2.07 (d, $J=3$ Hz, 1H), 2.0–1.8 (m, 3H), 1.7–1.55 (m, 2H), 1.5–1.2 (m, 8H); MS (APCI) m/z; 439 and 437 $(M-H)^-$.

9β-Chloro-9-deoxy-16-(3-methoxymethyl)phenyl-ω-tetranorPGF$_1$ 46a. To a stirred solution of **45a** (50 mg, 0.11 mmol) in MeOH (2 mL) was added 2 N NaOH (1 mL) at room temperature. The reaction mixture was stirred for 1 h, then poured into 1 N HCl and extracted with EtOAc twice. The combined organic layer was

washed with water and brine, then dried (Na_2SO_4). The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 20/1) to afford **46a** as a pale yellow oil (48 mg, 98%). IR (neat) 3600–3200, 2928, 2856, 1708, 1446, 1383, 1194, 1087, 1033, 970, 791, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.34–7.09 (m, 4H), 5.62 (dd, $J=15.4$, 5.8 Hz, 1H), 5.47 (dd, $J=15.4$, 7.6 Hz, 1H), 4.44 (s, 2H), 4.43–4.32 (m, 1H), 4.12–3.90 (m, 2H), 3.41 (s, 3H), 2.95–2.73 (m, 2H), 2.32 (t, $J=6.9$ Hz, 2H), 2.28–1.77 (m, 4H), 1.72–1.52 (m, 2H), 1.52–1.16 (m, 11H); MS (APCI) m/z: 437 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{24}H_{35}ClO_5+Na^+$: 461.2071; found: 461.2034.

9β-Chloro-9-deoxy-16-(4-hydroxy-3-methyl)phenyl-ω-tetranorPGF$_1$ 46c. 97% yield; IR (KBr) 3363, 2934, 1698, 1436, 1261, 1082, 976, 818 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 6.87 (d, $J=2$ Hz, 1H), 6.80 (dd, $J=8$, 2 Hz, 1H), 6.62 (d, $J=8$ Hz, 1H), 5.49 (dd, $J=15$, 6 Hz, 1H), 5.40 (dd, $J=15$, 8 Hz, 1H), 4.19 (q, $J=6$ Hz, 1H), 3.98 (q, $J=7$ Hz, 1H), 3.95 (q, $J=7$ Hz, 1H), 2.78 (dd, $J=13$, 6 Hz, 1H), 2.58 (dd, $J=13$, 7 Hz, 1H), 2.27 (t, $J=8$ Hz, 2H), 2.15 (s, 3H), 2.2–2.1 (m, 2H), 2.0–1.9 (m, 1H), 1.8–1.7 (m, 1H), 1.65–1.5 (m, 2H), 1.4–1.2 (m, 8H); MS (APCI) m/z: 425 and 423 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{23}H_{33}ClO_5+Na^+$: 447.1914; found: 447.1939.

16-(3-Methoxymethyl)phenyl-5-thia-ω-tetranorPGF$_1$ methyl ester 11,15-bis(tetrahydropyranyl) 47. Preparation of **47** was accomplished by another method, which was required for the synthesis of several 5-thiaPGE1 derivatives from THP-lactone. The details of this newly discovered method for large-scale synthesis will be reported in due course. ^1H NMR (300 MHz, $CDCl_3$): δ 7.3–7.1 (m, 4H), 5.65–5.3 (m, 2H), 4.75–4.45 (m, 2H), 4.43 and 4.42 (s, 2H), 4.3–3.7 (m, 4H), 3.67 (s, 3H), 3.5–3.4 and 3.3–3.2 (m, 2H), 3.38 (s, 3H), 3.0–2.7 (m, 2H), 2.6–2.1 (m, 7H), 2.0–1.4 (m, 17H).

16-(3-Methoxymethyl)phenyl-9-*O*-mesyl-5-thia-ω-tetranorPGF$_1$ methyl ester 11,15-bis(tetrahydropyranyl) 48a. To a stirred solution of **47** (630 mg, 1.0 mmol) and triethylamine (0.21 mL, 1.5 mmol) in CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (0.093 mL, 1.2 mmol) at 0 °C. The reaction mixture was stirred for 30 min, diluted with ether, and successively washed with water, 1 N HCl, aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). The solvent was removed by evaporation to give crude **48a**, which was used for the next reaction without further purification.

9β-Fluoro-9-deoxy-16-(3-methoxymethyl)phenyl-5-thia-ω-tetranorPGF$_1$ methyl ester 11,15-bis(tetrahydropyranyl) 49a. A mixture of crude **48a** and anhydrous tetrabutylammonium fluoride (prepared by concentration of 1.0 M THF solution, 0.30 g, 1.16 mmol) in anhydrous toluene (6.0 mL) was stirred at 55 °C for 1 h. The reaction mixture was cooled to room temperature, then poured into water and extracted with EtOAc. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed by evaporation to give **49a** (0.90 g), which was used for the next reaction without further purification.

9β-Fluoro-9-deoxy-16-(3-methoxymethyl)phenyl-5-thia-ω-tetranorPGF$_1$ methyl ester 50a. A mixture of **49a** (0.90 g) and $TsOH\cdot H_2O$ (10 mg) in MeOH (3 mL) was stirred at room temperature for 15 min. The reaction mixture was diluted with EtOAc and washed with water and brine, and dried (Na_2SO_4). The solvent was removed by evaporation and the residue was purified by short column chromatography on silica gel (EtOAc/hexane, 3/1) to remove polar by-products. The combined fractions were evaporated and the residue was further purified by passage through a Lobar column (Merck, sizeA, EtOAc/hexane, 7/3 to EtOAc) to give **50a** as a colorless oil (68 mg, 15% in three steps). IR (neat) 3397, 2922, 1735, 1437, 1365, 1193, 1092, 1032, 790, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 5.66 (dd, $J=15$, 6 Hz, 1H), 5.49 (dd, $J=15$, 8 Hz, 1H), 4.85–4.8 and 4.7–4.65 (m, 1H), 4.42 (s, 2H), 4.45–4.35 (m, 1H), 4.05–3.9 (m, 1H), 3.68 (s, 3H), 3.42 (s, 3H), 2.95–2.8 (m, 2H), 2.7–2.4 (m, 7H), 2.4–2.2 (m, 1H), 2.1–1.5 (m, 8H); MS (APCI) m/z: 437 $(M-H_2O+H)^+$.

9β-Fluoro-9-deoxy-16-(3-methoxymethyl)phenyl-5-thia-ω-tetranorPGF$_1$ 51a. To a stirred solution of **50a** (65 mg, 0.14 mmol) in MeOH (2 mL) was added 2 N NaOH (1 mL) at room temperature. The reaction mixture was stirred for 1 h, then poured into 1 N HCl and extracted with EtOAc. The organic layer was washed with water and brine, then dried (Na_2SO_4). The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50/1 to 20/1) to afford **51a** as a colorless oil (55 mg, 87%). IR (neat) 3376, 2924, 1712, 1446, 1381, 1192, 1091, 1033, 971, 915, 791, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.3–7.1 (m, 4H), 5.68 (dd, $J=15$, 6 Hz, 1H), 5. 51 (dd, $J=15$, 9 Hz, 1H), 4.9–4.6 (m, 1H), 4.44 (s, 2H), 4.42 (q, $J=6$ Hz, 1H), 3.96 (q, $J=9$ Hz, 1H), 3.42 (s, 3H), 3.8–2.6 (br, 3H), 2.90 (dd, $J=14$, 6 Hz, 1H), 2.82 (dd, $J=14$, 6 Hz, 1H), 2.65–2.2 (m, 7H), 2.1–1.5 (m, 7H); MS (APCI) m/z: 439 $(M-H)^-$; HRMS (MALDI-TOF) calcd for $C_{23}H_{33}FO_5S+Na^+$: 463.1930; found: 463.1965.

Prostanoid EP and IP receptor binding assay

Membranes from CHO cells expressing prostanoid receptors were incubated with radioligand (2.5 nM of [^{3}H]PGE_2 for EP1-4 or 5.0 nM of [^{3}H]Iloprost for IP) and the test compounds at various concentrations in assay buffer [10 mM Kpi (KH_2PO_4, KOH; pH 6.0), 1 mM EDTA and 0.1 mM NaCl, for EP1–4-receptors; 50 mM Tris–HCl (pH 7.5), 1 mM EDTA and 10 mM $MgCl_2$ for IP-receptor]. Incubation was carried out at 25 °C for 60 min except for EP1 (20 min) and IP (30 min) receptors. The incubation was terminated by filtration through Whatman GF/B filters. The filters were then washed with ice-cold buffer [10 mM Kpi (KH_2PO_4, KOH; pH 6.0), 0.1 mM NaCl for EP1-4; 10 mM Tris–HCl (pH 7.5), 0.1 mM NaCl for IP], and the radioactivity on the filter was measured in 6mL of liquid scintillation (ACSII) mixture with a liquid scintillation counter. Nonspecific binding was determined by incubation of 10

μM unlabeled PGE_2 (for EP1-4) or 1 μM unlabeled Iloprost (for IP) with assay buffer.

Measurement of cAMP production

Chinese hamster ovary (CHO) cells expressing EP4-receptor were cultured in 24-well plates (1×10^5 cells/well). After 2 days, the medium was removed and cells were washed with 500 μL of Minimum Essential Medium (MEM) and pre-incubated for 10 min in 450 μL of assay buffer (MEM containing 1 mM of IBMX, 1% of BSA) at 37 °C. Then, the reaction was started with the addition of each test compound in 50 μL of assay buffer. After incubation for 10 min at 37 °C, the reaction was terminated by addition of 500 μL of ice-cold 10% trichloroacetic acid. cAMP production was measured by radio-immunoassay using a cAMP assay kit (Amersham).

Measurement of intracellular Ca^{2+} production

Intracellular Ca^{2+} concentration was measured using a Jasco CAM220 Spectrofluorometer. Chinese hamster ovary (CHO) cells expressing EP3-receptor were cultured for 2 days. After the medium was removed, the cells were washed with PBS and centrifuged at 800 rpm for 3 min. The cells were incubated at 37 °C for 60 min with fura 2-AM in conditioned medium consisting of MEM containing 20 μM indomethacin, 10% FCS and 10 mM HEPES–NaOH (pH 7.4). The medium containing the cells was centrifuged at 800 rpm for 3 min and the cells were suspended in assay buffer consisting of MEM containing 2 μM indomethacin, 0.1% BSA and 10 mM HEPES–NaOH (pH 7.4). The test compound was added to the suspension of the cells with stirring. Intracellular Ca^{2+} production was calculated from the ratio of the fluorescence intensities at 340 and 380 nm.

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