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Design and Synthesis of a Selective EP4-Receptor Agonist. Part 1: Discovery of 3,7-DithiaPGE$_1$ Derivatives and Identification of Their ω Chains

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Abstract—Improvement of EP4-receptor selectivity and the agonist activity by introduction of heteroatoms into the α chain of PGE$_1$ was investigated. Among the compounds tested, 3,7-dithiaPGE$_1$ **4a** exhibited good EP4-receptor selectivity and agonist activity. Further modification of the ω chain of 3,7-dithiaPGE$_1$ was performed to improve EP4-receptor selectivity and agonist activity. Of the compounds produced, 16-phenyl-ω-tetranor-3,7-dithiaPGE$_1$ **4p** possessing moderate EP4-receptor selectivity and agonist activity, was identified as a new chemical lead for further optimization by modification of the aromatic moiety.

Introduction

Prostaglandins have been known to have diverse biological activities that are mediated by all the receptor subtypes.[1] The EP4-receptor subtype, which is located in thymus, lung, heart, kidney, bone, womb, liver and other organs, has been characterized with relaxation of the porcine and dog saphenous vein and of the rabbit jugular vein.[2] The biological effects have been considered to be correlated with an enhancement of the intracellular cAMP concentration. Novel biological roles of the EP4-receptor are expected to be revealed by experiments using subtype selective ligands. Some PG congeners have been used as probes for EP4-receptor ligands,[3] however, their subtype selectivities were poor. As such, identification of a highly selective EP4-receptor agonist is an attractive approach to disclose the biological role of the EP4-receptor and develop clinically useful drugs.

In the course of a screening program to find an EP4-receptor selective agonist, 7-thia PGE$_1$ derivative **3** was found to exhibit potent affinity for EP4-receptor although it also showed affinities for other receptors. Chemical modification of **3** was carried out with the introduction of another heteroatom into the α chain and further chemical development (Scheme 1). In this report, we describe identification and biological evaluation of 3,7-dithiaPGE$_1$ derivatives as new selective EP4-receptor agonists. Structure–activity relationships (SARs) are also discussed.

Chemistry

The 7-thiaPGE analogues described here were synthesized according to the method[4] reported previously with minor modifications. Synthesis of 4,7-dithiaPGE$_1$ is outlined in Scheme 2. Monoalkylation of ethanedithiol **6** afforded **7**. Ring opening reaction of the epoxide **8**[4] with **7** followed by dehydration provided **9**. Conjugate addition reaction of higher order vinyl cuprate prepared from commercially available vinyliodide **10a** and lithium (2-thienyl)cyanocuprate[5] to the enone **9** gave **11**. Deprotection of *t*-butyldimethylsilyl (TBS) groups of **11** afforded **12**. Enzymatic hydrolysis of **12** with porcine liver esterase (PLE) in phosphate buffer provided **13**.

Synthesis of 3,6-dithiaPGE$_1$ **19** is outlined in Scheme 3. Treatment of 1,2-ethanedithiol **6** with dibutyltin oxide in benzene afforded **14**, monoalkylation of which pro-

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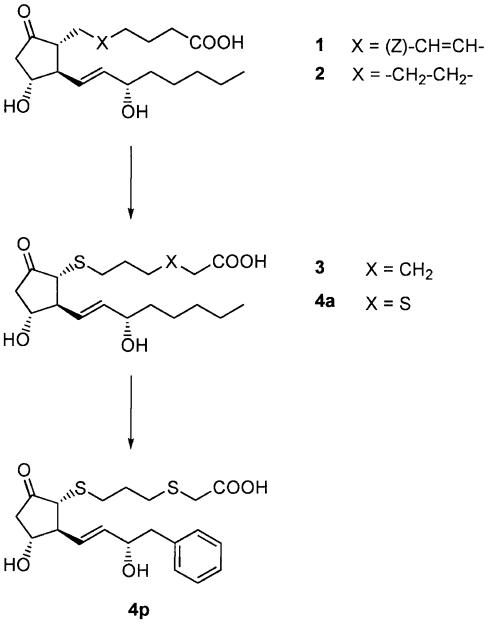
vided **15**. Conjugate addition of **15** to the enone **16**[5,6] in the presence of piperidine gave **17**, TBS groups of which were deprotected to afford **18**. Enzymatic hydrolysis of **18** provided 3,6-dithiaPGE$_1$ **19**.



Scheme 1. Discovery of 16-phenyl-ω-tetranor-3,7-dithiaPGE$_1$ **4p**.

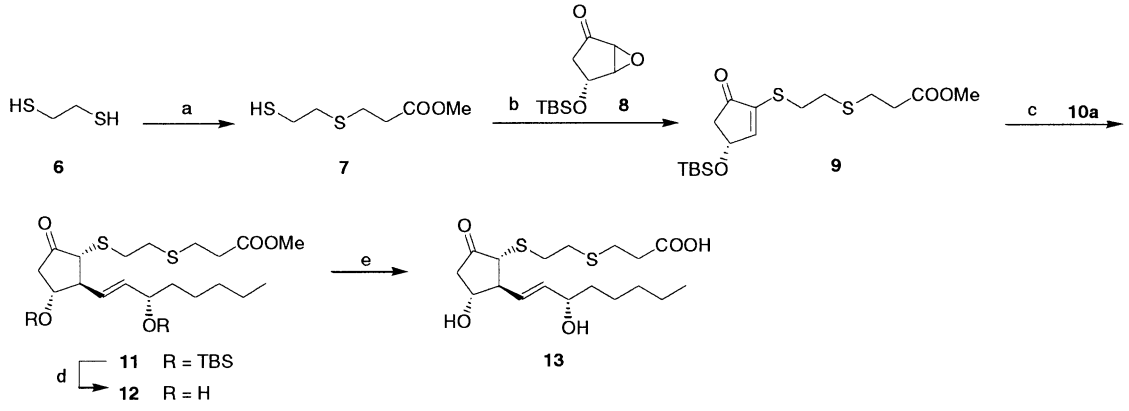
Synthesis of 3-oxa-7-thiaPGE$_1$ is outlined in Scheme 4. *O*-Alkylation of 3-bromopropanol **20** afforded **21**, substitution of which with thiourea followed by hydrolysis provided the thiol **22**. Ring opening of the epoxide **8** with **22** in the presence of alumina afforded **23**, which was converted to **26** according to the same procedures as described for the synthesis of **13** from **9**.

Syntheses of 3,7-dithiaPGE$_1$ are outlined in Schemes 5 and 6. Treatment of 1,3-propanedithiol **27** with dibutyltin oxide in benzene afforded **28**, monoalkylation of which with methyl bromoacetate provided **29**. Ring opening reaction of the epoxide **8** with the thiol **29** followed by dehydration provided **30**. Compound **30** was converted to **4a–r** and **36a–c** according to the same procedure as described for the synthesis of **13**.

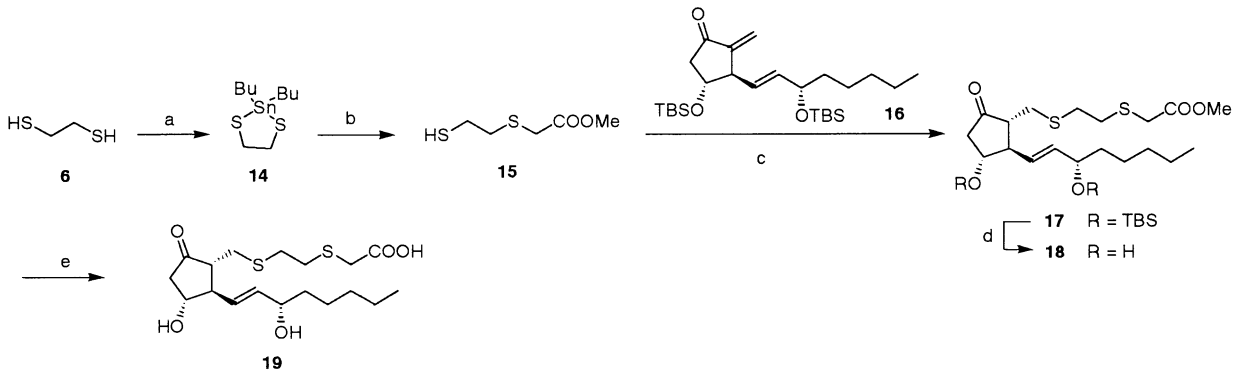
The optically active vinyl iodides **10** were prepared from racemic allyl alcohols by the Sharpless kinetic resolution,[7] except for the commercially available product.

Results and Discussion

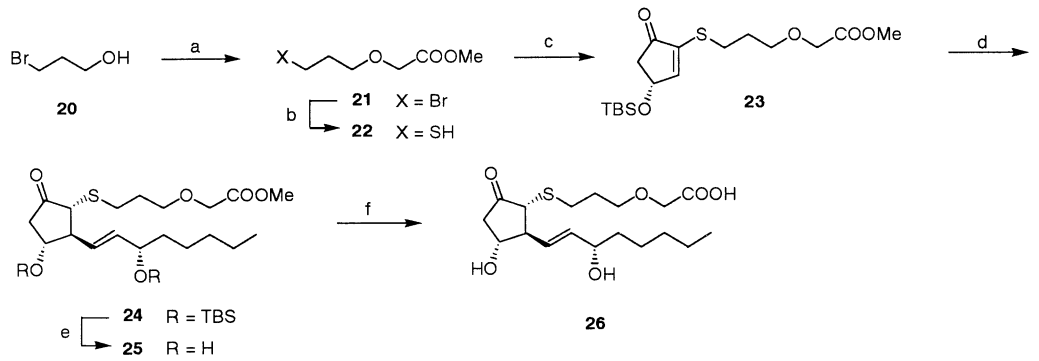
The effects of introduction of heteroatom(s) such as oxygen and sulfur atoms into the α chain of PGE$_1$ on EP4-receptor selectivity and agonist activity were investigated. Among the compounds tested, 3,7-dithiaPGE$_1$ **4a** exhibited good EP4-receptor selectivity and agonist



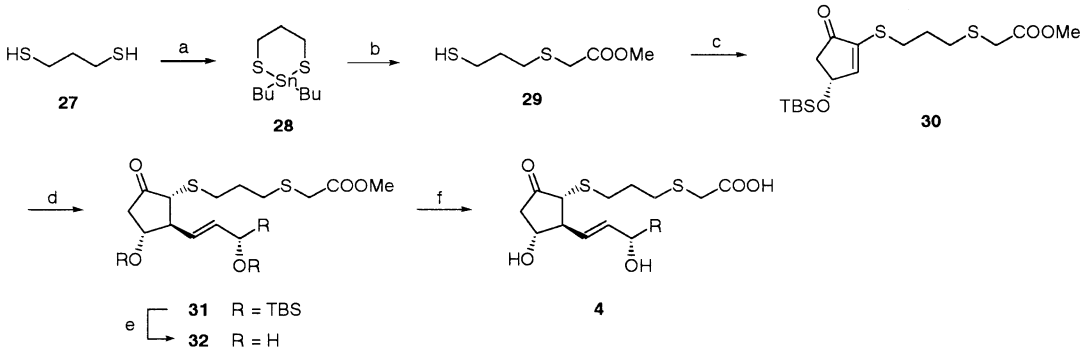
Scheme 2. Synthesis of 4,7-dithiaPGE$_1$ **13**. Reagents: (a) methyl acrylate, piperidine, EtOH; (b) **8**, alumina, hexane; (c) **10a**, *t*-BuLi, lithium 2-thienylcyanocuprate, THF, ether; (d) (HF)$_n$-py, pyridine, CH_3CN; (e) PLE, EtOH, phosphate buffer.

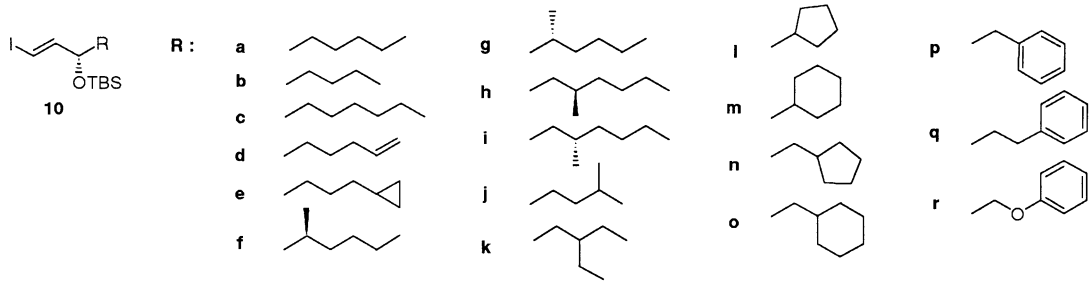


Scheme 3. Synthesis of 3,6-dithiaPGE$_1$ **20**. Reagents: (a) dibutyltinoxide, benzene; (b) methyl bromoacetate, DMF; (c) piperidine, MeOH; (d) (HF)$_n$-py, pyridine, CH_3CN; (e) PLE, EtOH, phosphate buffer.

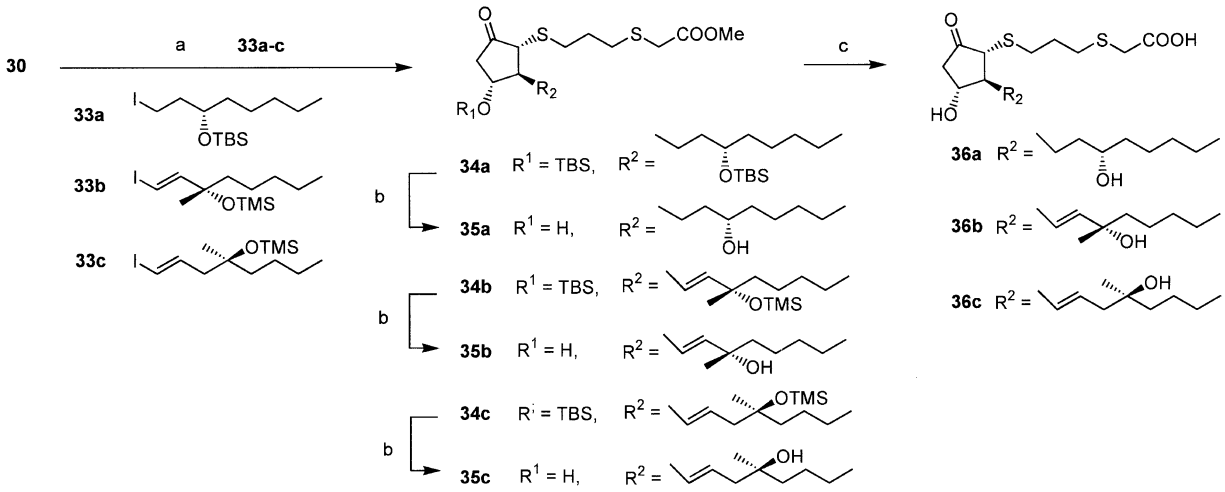


Scheme 4. Synthesis of 3-oxa-7-thiaPGE$_1$ **26**. Reagents: (a) methyl bromoacetate, NaH, DMF; (b) thiourea, EtOH, then 1 N NaOH, 1 N HCl; (c) **8**, alumina, hexane; (d) **10a**, *t*-BuLi, lithium 2-thienylcyanocuprate, ether, THF; (e) $(HF)_n$-py, pyridine, CH_3CN; (f) PLE, EtOH, phosphate buffer.





Scheme 5. Synthesis of 3,7-dithiaPGEs **4a**–**r**. Reagents: (a) dibutyltinoxide, benzene; (b) methyl bromoacetate, DMF; (c) **8**, alumina, hexane; (d) **10**, *t*-BuLi, lithium 2-thienylcyanocuprate, ether, THF; (e) $(HF)_n$-py, pyridine, CH_3CN; (f) PLE, EtOH, phosphate buffer.



Scheme 6. Synthesis of 3,7-dithiaPGE$_1$ possessing miscellaneous ω chain **36a**–**c**. Reagents: (a) **33a**–**c**, *t*-BuLi, lithium 2-thienylcyanocuprate, ether, THF; (b) $(HF)_n$-py, pyridine, CH_3CN; (c) PLE, EtOH, phosphate buffer.

activity as shown in Table 1. Although the selectivity (K_iEP3/K_iEP4) was excellent, **4a** showed potent EP3-receptor agonist activity for its described K_i value. Chemical modification of the ω chain of 3,7-dithiaPGE$_1$ was continued to further improve both of EP4-receptor selectivity and agonist activity. Of the resulting compounds, 16-phenyl-ω-tetranor-3,7-dithiaPGE$_1$ **4p** with moderate EP4-receptor selectivity and agonist activity was identified as a new chemical lead for further optimization because of the ease of further modification of its aromatic moiety (Scheme 1).

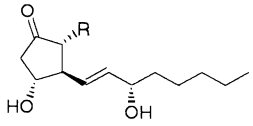
Binding assay was conducted according to the reported method[8] with minor modifications. The binding constants were determined by competitive binding assay of the test compounds using radiolabeled ligands such as [^{3}H] PGE$_2$ (EP-receptors) and [^{3}H] Iloprost (IP-receptor).

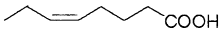
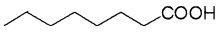
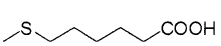
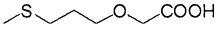
Agonist activities of the compounds for EP4-receptor and EP3-receptor were evaluated based on their effects on intracellular cAMP production using EP4-receptor expressing CHO cells and on intracellular Ca^{2+} concentration using EP3-receptor expressing CHO cells, respectively.

We began our molecular design with introduction of heteroatoms into the α chain of PGE$_1$ because 7-thiaPGE$_1$ analogue **3** exhibited better EP4-receptor selectivity than PGE$_1$ **2** or PGE$_2$ **1**. As shown in Table 1, 7-thiaPGE1 demonstrated affinity not only to the EP3-receptor but also to the IP-receptor. For its relatively weak affinity (K_i = 870 nM) to the IP-receptor, **3** showed potent agonist activity (EC_{50} = 26 nM). Since both of the subtypes (EP4 and IP) are involved in increases in intracellular cAMP concentration, it was important to remove the IP-receptor agonist activity in **3** to disclose the physiological roles of the EP4-receptor. According to our internal data,[9] 3-thiaPGE$_1$ did not show affinity to the IP-receptor at 10 μM. As such, structural hybridization of these thiaPGE analogues was expected to be effective to remove the IP-receptor affinity from 7-thiaPGE$_1$ analogues.

Introduction of another sulfur atom into position-3 of **3** provided **4a** with no affinity to the IP-receptor. Besides, **4a** was found to demonstrate a markedly increased EP4-receptor selectivity maintaining excellent EP4-receptor agonist activity. On the other hand, the corresponding 3-oxa-analogue **26** exhibited less EP4-receptor selectivity. As illustrated in the profile of **13**, introduction of another sulfur atom into position-4 of **3** did not improve the EP4-receptor selectivity to the EP3-receptor (K_iEP3/K_iEP4 = 1.3) with marked loss of the agonist activity. Shifting the sulfur atom at position-7 of **4a** to position-6 (**19**) resulted in marked reduction of the

Table 1. Optimization of α chain



Compound	R	Binding K_i (nM)					EC_{50} (nM)
		mEP1	mEP2	mEP3	mEP4	hIP	mEP4
1		6.0	22	5.0	3.1	$>10^4$	3.6
2		22	41	5.0	3.3	150	2.5
3		120	100	4.5	0.7	870	3.7
13		610	1200	4.4	3.2	$>10^4$	170
19		50	1000	3.5	28	$>10^4$	7800
26		1200	150	11	2.3	510	7.7
4a		610	280	220	0.7	$>10^4$	4.3

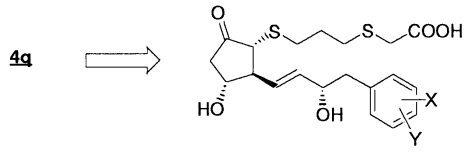
Using membrane fractions of CHO cells expressing the prostanoid receptors, the mouse (m) EP-receptor or human (h) IP-receptor, K_i values were determined by competitive binding assay, which was performed according to the method of Kiriyama et al. with some modifications.[8] With regard to the subtype-receptor agonist activity, EC_{50} values were determined based on the effects of the test compounds on the increase in intracellular cAMP production in EP4 receptor expressing cells.

agonist activity. The EP4-receptor selectivity was also markedly deteriorated (K_iEP3/K_iEP4 = 0.13). The EP1 and EP3 receptor affinities were restored by this modification. 3,7-DithiaPGE$_1$ **4a** seemed to be the most potent and most selective of the series as described in Table 1. However, the EP3-receptor agonist activity of **4a** (EC_{50} = 1.1 nM) was fairly potent for its described K_i value. Thus, the α chain with a 3,7-dithia moiety might be one of the most promising entries for chemical synthesis for the development of selective EP4-receptor agonists.

For the purpose of further optimization of the EP4-receptor agonist, we focused our attention on chemical modification of the ω chain of **4a** because there have been many successful examples of ω-chain modification to improve biological activities of PG derivatives. As described in Table 2, replacement of the 15-*n*-pentyl moiety with a butyl, hexyl, 4-pentenyl and 3-cyclopropylpropyl groups afforded **4b**, **4c**, **4d** and **4e**, respectively. All four analogues demonstrated increased EP3-receptor affinity relative to **4a**, while they showed similar EP4-receptor affinity. Their EP4-receptor agonist activity was not markedly affected by this chemical modification except in the case of **4c**. Introduction of a 16(*S*)- or 16(*R*)-methyl moiety[10] into **4a** provided **4f** and **4g**, respectively, which decreased the EP4-receptor selectivity although they retained potent agonist activity. In the case of 16(*S*)-methyl derivative **4f**, however, EP4-receptor selectivity (K_iEP3/K_iEP4) was preserved to some extent. Reduction of the EP4-receptor selectivity was also observed by the introduction of a 17(*R*)- or 17(*S*)-methyl moiety.[4,11] Replacement of the 15-pentyl moiety of **4a** with a 3-methylbutyl or 2-ethylbutyl group afforded **4j** and **4k**, respectively, without improvement of the EP4-receptor selectivity especially to the EP3-receptor. Both the 15-cyclopentyl and 15-cyclohexyl[4,12] derivatives **4l** and **4m** demonstrated the most reduced EP4-receptor affinity and agonist activity. 16-Cyclopentyl and 16-cyclohexyl derivatives **4n** and **4o** exhibited 6-fold less potent EP4-receptor affinity than **4a** without improvement of their EP4-receptor selectivity to their EP3-receptor. 16-Phenyl derivative[13] **4p** demonstrated moderate EP4-receptor selectivity with moderate agonist activity. 17-Phenyl derivative[14] **4q** and 16-phenoxy derivative[15] **4r** showed more potent affinity for the EP3-receptor than the EP4-receptor.

13,14-Dihydro-3,7-dithiaPGE$_1$ **36a**, 15(*S*)-methyl-3,7-dithiaPGE$_1$ derivative **36b** and 16(*R*)-methyl-16(*S*)-hydroxy-15-deoxy-3,7-dithiaPGE$_1$[16] **36c** were prepared and biologically evaluated (Table 3). Hydrogenation of the 13,14-double bond of **4a** gave **36a** with a marked increase in EP3-receptor affinity, while its agonist activity was less potent than **4a**. Introduction of a 15(*S*)-methyl group into **4a** provided **36b**, which showed reduced EP3/EP4-receptor selectivity. Shifting the two functional groups of position-15 in **36b** to position-16 afforded **36c** without improvement of the selectivity (K_iEP3/K_iEP4 = 1). Among them, **36b** exhibited the good EP4-receptor selectivity and agonist activity.

In summary, we have identified 3,7-dithiaPGE$_1$ **4a** as a unique chemical lead to restart our chemical modification to find a new EP4-receptor agonists. Detailed structural modification of the ω chain in **4a** led to the discovery of a new chemical lead **4p**, which demonstrated a balanced profile with regard to receptor selectivity, agonist activities[17] (EC_{50}: EP3 = 530 nM, EP4 = 34 nM) and the ease of further modification of the phenyl moiety as illustrated in Scheme 7. Further optimization of **4p** to obtain more potent and selective EP4-receptor agonists will be reported in the following paper.



Scheme 7. Plausible modification of the aromatic moiety of **4q**.

Experimental

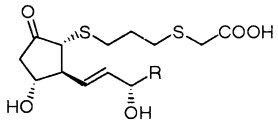
General procedures

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 or VXR-200s spectrometer using deuterated chloroform ($CDCl_3$) or deuterated methanol (CD_3OD) as the solvent. Fast atom bombardment mass spectra (FAB-MS) and electron ionization (EI) were obtained on a JEOL JMS-DX303HF spectrometer. Atmospheric pressure chemical ionization (APCI) was determined on a Hitachi M1200H spectrometer. Infrared spectra (IR) were measured on a Perkin-Elmer FT-IR 1760× 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), chloroform ($CHCl_3$), methanol (MeOH), acetic acid (AcOH), pyridinium poly(hydrogen fluoride) [$(HF)_n$·py, Aldrich], porcine liver esterase (PLE).

Methyl 6-mercapto-4-thiahexanate 7. To a stirred mixture of 1, 2-ethanedithiol (1.17 g, 12.4 mmol) and methyl acrylate (1.67 mL, 18.6 mmol) was added piperidine (0.05 mL) at room temperature (exothermic). Stirring was continued for 5 min until the exothermic reaction subsided. The reaction mixture was directly subjected to column chromatography on silica gel (EtOAc/hexane, 1:10–1:7) to afford **7** as a colorless oil (1.06 g, 47%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (s, 3H), 2.85–2.60 (m, 8H).

2-(6-Carbomethoxy-1, 4-dithiahexyl)-4-(*R*)-*t*-butyldimethylsilyloxy-2-cyclopentenone 9. A solution of epoxide **8** and thiol **7** (235 mg, 1.3 mmol) in hexane (10 mL) and

Table 2. Effect of the chemically modified ω chain on biological activites



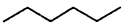
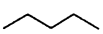
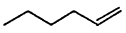
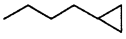
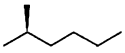
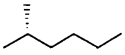
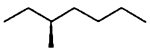
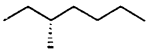
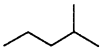
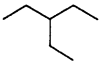
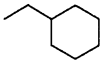
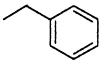
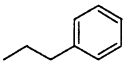
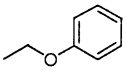
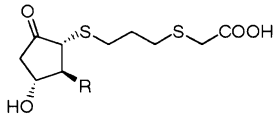
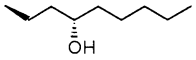
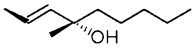
Compound	R	Binding K_i (nM)					EC_{50} (nM)
		mEP1	mEP2	mEP3	mEP4	hlP	mEP4
4a		610	280	220	0.7	$>10^4$	4.3
4b		530	800	23	1.4	$>10^4$	3.9
4c		240	94	2.5	0.3	1100	24
4d		2100	300	6.8	1.6	$>10^4$	10
4e		760	130	4.7	0.4	Not tested	2.1
4f		110	250	25	0.2	680	0.8
4g		3500	150	2.1	0.2	Not tested	1.4
4h		940	83	10	0.8	350	1.4
4i		15	110	4.5	0.6	220	18
4j		2500	840	22	1.9	Not tested	32
4k		250	540	50	8.5	$>10^4$	140
4l		$>10^4$	3000	660	74	$>10^4$	600
4m		1200	390	610	22	1400	1300
4n		$>10^4$	3900	47	4.2	$>10^4$	55
4o		610	7000	83	4.2	$>10^4$	140
4p		2600	3900	130	7	$>10^4$	34
4q		360	$>10^4$	4.6	6.0	$>10^4$	69
4r		45	$>10^4$	4.3	12	$>10^4$	Not tested.

Table 3. Biological evaluation of 3,7-dithia PGE_1 possessing miscellaneous ω chains



Compound	R	Binding K_i (nM)					EC_{50} (nM)
		mEP1	mEP2	mEP3	mEP4	hlP	mEP4
36a		310	1200	8.3	1.6	$>10^4$	84
36b		310	850	34	0.7	$>10^4$	2.2
36c		$>10^4$	330	6.3	5.6	$>10^4$	Not tested

CH_2Cl_2 (1 mL) was stirred at room temperature in the presence of activated alumina (1 g). After the reaction was completed, alumina was removed by filtration and washed repeatedly with CH_2Cl_2. The filtrate was evaporated and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give **9** as a colorless oil (389 mg, 77%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.90 (d, $J=2$ Hz, 1H), 5.0–4.9 (m, 1H), 3.72 (s, 3H), 3.1–3.0 (m, 2H), 2.95–2.75 (m, 5H), 2.7–2.6 (m, 2H), 2.36 (d, $J=18$ Hz, 1H), 0.92 (s, 9H), 0.16 (s, 6H).

4,7-DithiaPGE_1 methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 11. To a stirred solution of 3-(*S*)-*t*-butyldimethylsilyloxy-1-iodo-1-octene **10a** (188 mg, 0.51 mmol) in freshly distilled dry diethylether (4 mL) was slowly added *t*-butyllithium (1.57 M in pentane, 0.65 mL, 1.02 mmol) at −70 °C under Ar and stirring was continued for 1 h at that temperature. To the resulting suspension was added dropwise lithium 2-thienylcyanocuprate (0.25 M in THF, 2.0 mL, 0.51 mmol) in 5 min. The gray suspension was stirred for an additional 25 min and 2-(6-carbomethoxy-3-oxa-1-thiahexyl)-4-(*R*)-*t*-butyldimethylsilyloxy-2-cyclopentenone **9** (200 mg, 0.51 mmol) in THF (3 mL) was added dropwise in 8 min. The resulting yellowish mixture was allowed to warm to −20 °C over 1 h and then poured into a mixture of hexane (10 mL) and saturated aqueous NH_4Cl (10 mL) under stirring. The separated organic layer was washed with aqueous NH_4Cl, H_2O and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/10–1/6) to afford **11** as a pale yellow oil (151 mg, 47%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.4 (m, 2H), 4.2–4.0 (m, 2H), 3.68 (s, 3H), 3.0–2.3 (m, 12H), 1.6–1.2 (m, 8H), 1.0–0.8 (m, 21H), 0.1–0.0 (m, 12H).

4,7-DithiaPGE_1 methyl ester 12. A stirred solution of **11** (148 mg, 0.23 mmol) and pyridine (0.5 mL) in acetonitrile (5 mL) was cooled in an ice-bath and treated with $(HF)_n$·py (Aldrich, 0.5 mL). After stirring for 3 h at room temperature, the reaction mixture was slowly poured into saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc twice and the EtOAc layer was washed with 1 N HCl, H_2O and brine, and dried over Na_2SO_4. After removal of the solvent by evaporation, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/1–3/1–1/0) to give **12** as a pale brown oil (56 mg, 60%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.6 (m, 2H), 4.5–4.4 and 4.25–4.10 (m, 2H), 3.71 (s, 3H), 3.5–3.4 and 3.1–2.2 (m, 12H), 1.7–1.2 (m, 8H), 0.90 (t, $J=7$ Hz, 3H).

4,7-DithiaPGE_1 13. To a stirred mixture of **13** (54 mg, 0.13 mmol) in ethanol (1 mL) and phosphate buffer (pH 7.4, 5 mL) was added porcine liver esterase (PLE) (Sigma, 20,000 U, 0.1 mL) at room temperature. The reaction mixture was stirred vigorously for 1.5 h. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ solution and then extracted with EtOAc twice, dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica gel (EtOAc/hexane, 1/1–EtOAc/hexane/AcOH, 30/10/1–EtOAc/AcOH, 40/1) provided **13** as a pale yellow oil (48 mg, 95%). IR (neat) 3392, 2930, 2859, 1734, 1407, 1246, 1150, 1079, 969 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85–5.55 (m, 2H), 4.8–4.0 (br, 3H), 4.25–4.05 (m, 2H), 3.55–3.45 and 3.2–2.2 (m, 12H), 1.7–1.2 (m, 8H), 0.91 (t, $J=7$ Hz, 3H); MS (FAB) m/z 373 $(M-H_2O+H)^+$.

2,2-Dibutyl-[1,3,2]dioxastannolane 14. A solution of 1,2-ethanedithiol (1.0 g, 10.6 mmol) and dibutyltinoxide (2.64 g, 10.6 mmol) in benzene (10 mL) was stirred under reflux for 48 h. After the reaction was completed, the solvent was removed by evaporation to give **14** as a white solid (3.37 g, 98%).

Methyl 5-mercapto-3-thiapentanoate 15. To a stirred solution of **14** (500 mg, 1.54 mmol) in DMF (5 mL) was added methyl bromoacetate (283 mg, 1.85 mmol) at room temperature under Ar. The reaction mixture was stirred at 100 °C for 5 h. After cooling to room temperature, the reaction mixture was treated with water and stirred for 1 h. The mixture was extracted with EtOAc and the organic layer was washed with brine, and dried over Na_2SO_4. After removal of solvents by evaporation, the residue was purified by column chro-

matography on silica gel (EtOAc/hexane, 1/20–1/10) to afford **15** as a colorless oil (210 mg, 82%).

4, 6-DithiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 17. To a stirred solution of **16** (211 mg, 0.45 mmol) and **15** (50 mg, 0.30 mmol) in MeOH (4 mL) was added two drops of piperidine at −78 °C under Ar. The reaction mixture was stirred at that temperature for 5 min, at 0 °C for 10 min and then diluted with EtOAc. The solution was washed with water, brine and dried (Na_2SO_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 **17** as a colorless oil (110 mg, 60%). ^{1}H NMR (200 MHz, $CDCl_3$); δ 5.65 (dd, J = 15, 7 Hz, 1H), 5.50 (dd, J = 15, 8 Hz, 1H), 4.10 (m, 2H), 3.74 (s, 3H), 3.26 (s, 2H), 2.96–2.57 (m, 8H), 2.22 (m, 2H), 1.6–1.1 (m, 8H), 0.88 (m, 21H), 0.05 (m, 12H).

4,7-DithiaPGE$_1$ methyl ester 18. A stirred solution of **17** (94 mg, 0.15 mmol) and pyridine (0.4 mL) in acetonitrile (4 mL) was cooled in an ice-bath and treated with $(HF)_n$·py (Aldrich, 0.8 mL). The reaction mixture was stirred for 2 h at room temperature and then slowly poured into saturated aqueous $NaHCO_3$ solution. Then, the mixture was extracted with EtOAc twice and the organic layer was washed with 1 N HCl, H_2O and brine, and dried over Na_2SO_4. After removal of solvent by evaporation, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 1/0–50/1–25/1) to give **12** as a pale yellow oil (50 mg, 85%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.75 (1H, dd, J = 15, 7 Hz), 5.59 (1H, dd, J = 15, 8 Hz), 4.12 (m, 2H), 3.75 (s, 3H), 3.26 (s, 2H), 3.2–2.6 (m, 8H), 2.28 (m, 2H), 1.8–1.2 (m, 8H), 0.90 (3H, t, J = 6 Hz); MS (APCI) m/z 387 $(M-H_2O+H)^+$.

4, 6-DithiaPGE$_1$ 19. To a stirred mixture of **18** (40 mg, 0.10 mmol) in ethanol (0.5 mL) and phosphate buffer (pH 7.4, 5 mL) was added PLE (0.1 mL) at room temperature. The reaction mixture was stirred vigorously for 1.5 h and the resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$. The reaction mixture was extracted with EtOAc twice, dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica gel ($CHCl_3$/MeOH, 20/1–9/1) provided **19** as a pale yellow oil (48 mg, 95%). IR (neat) 3391, 2929, 2858, 2649, 1739, 1407, 1277, 1157, 1075, 973, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.76 (dd, J = 15, 7 Hz, 1H), 5.63 (dd, J = 15, 8 Hz, 1H), 4.4 (br, 3H), 4.14 (m, 2H), 3.25 (s, 2H), 3.05–2.55 (m, 8H), 2.45–2.20 (m, 2H), 1.8–1.1 (m, 8H), 0.89 (t, J = 6 Hz, 3H); MS (FAB) m/z 373 $(M-H_2O+H)^+$.

Methyl 6-bromo-3-oxahexanate 21. To a stirred solution of 3-bromo-1-propanol **20** (1.33 g, 9.6 mmol) and methyl bromoacetate (1.47 g, 9.6 mmol) in dry DMF (10 mL) was added sodium hydride (60% in oil, 384 mg, 9.6 mmol) in several portions at 0 °C. After stirring for 2 h, the resulting yellow suspension was poured into ice-cooled 1 N HCl. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/8) to give **21** as a colorless oil (0.51 g, 25%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.10 (s, 2H), 3.76 (s, 3H), 3.67 (t, J = 7 Hz, 2H), 3.54 (t, J = 7 Hz, 2H), 2.25–2.10 (m, 2H); MS (APCI) m/z 213 $(M+H)^+$.

Methyl 6-mercapto-3-oxahexanate 22. A suspension of **21** (0.51 g, 2.4 mmol) and thiourea (0.46 g, 6.0 mmol) in ethanol (10 mL) was stirred under reflux for 5 h. The resulting clear solution was treated with 2 N NaOH (5.0 mL, 10 mmol) at that temperature and then stirred for 30 min. Then, the mixture was cooled to 0 °C and neutralized with 2 N HCl. The mixture was extracted with EtOAc repeatedly and the combined organic layer was washed with brine, and dried over $MgSO_4$. After removal of the solid by filtration, the filtrate was treated with CH_2N_2 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/6) to afford **22** as a colorless oil (147 mg, 37%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.09 (s, 2H), 3.74 (s, 3H), 3.63 (t, J = 7 Hz, 2H), 2.68 (q, J = 7 Hz, 2H), 1.91 (pent, J = 7 Hz, 2H), 1.43 (t, J = 7 Hz, 1H).

2-(6-Carbomethoxy-5-oxa-1-thiahexyl)-4-(*R*)-*t*-butyldimethylsilyloxy-2-cyclopentenone 23. A solution of epoxide **8** and thiol **22** (145 mg, 0.88 mmol) in hexane (10 mL) was stirred at room temperature in the presence of activated alumina (1 g). After the reaction was completed, alumina was removed by filtration and washed with CH_2Cl_2 repeatedly. The filtrate was evaporated and purified by column chromatography on silica gel (EtOAc/hexane = 1:4) to afford enone **23** as a colorless oil (202 mg, 61%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.86 (d, J = 2 Hz, 1H), 5.0–4.9 (m, 1H), 4.07 (s, 2H), 3.76 (s, 3H), 3.65 (t, J = 7 Hz, 2H), 2.97 (t, J = 7 Hz, 2H), 2.85 (dd, J = 19, 6 Hz, 1H), 2.37 (dd, J = 19, 2 Hz, 1H), 2.05–1.90 (m, 2H), 0.90 (s, 9H), 0.15 (s, 6H).

3-Oxa-7-thiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 24. To a stirred solution of 3-(*S*)-*t*-butyldimethylsilyloxy-1-iodo-1-octene **10a** (195 mg, 0.53 mmol) in freshly distilled dry diethyl ether (3 mL) was slowly added *t*-butyllithium (1.57 M in pentane, 0.68 mL, 1.06 mmol) at −70 °C under Ar. The reaction mixture was stirred for 1 h at that temperature. To the resulting suspension was added lithium 2-thienylcyanocuprate (0.25 M in THF, 2.2 mL, 0.53 mmol) dropwise over 5 min. The gray suspension was stirred for an additional 25 min and 2-(6-carbomethoxy-5-oxa-1-thiahexyl)-4-(*R*)-*t*-butyldimethylsilyloxy-2-cyclopentenone **23** (200 mg, 0.51 mmol) in THF (3 mL) was added dropwise in 8 min. The resulting yellowish mixture was allowed to warm to −20 °C over 1 h and then poured into a mixture of hexane (10 mL) and saturated aqueous NH_4Cl (10 mL) under stirring. The organic layer was washed with aq NH_4Cl, H_2O 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, 1/10–1/6) to afford **24** as a pale yellow oil (64 mg, 20%). ^{1}H NMR (200 MHz, CDCl3) δ 5.75–5.45 (m, 2H), 4.1-4.0 (m, 4H), 3.73 (s, 3H), 3.62 (t, J = 6 Hz, 2H), 2.9–2.5 (m, 5H), 2.38 (dd, J = 19, 8 Hz, 1H), 2.0–1.8 (m, 2H), 1.6–1.2 (m, 8H), 0.9–0.8 (m, 21H), 0.1–0.0 (m, 12H).

3-Oxa-7-thiaPGE$_1$ methyl ester 25. A solution of **24** (64 mg, 0.10 mmol) and pyridine (0.5 mL) in acetonitrile (5 mL) was cooled in an ice-bath and treated with $(HF)_n$·py (Aldrich, 0.5 mL). The reaction mixture was stirred for 3 h at room temperature and then slowly poured into saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with EtOAc twice and the EtOAc layer was washed with 1 N HCl, H_2O and brine, and dried over Na_2SO_4. After removal of solvent by evaporation, the residue was purified by column chromatography on silica gel (EtOAc/AcOH, 20/1) to give **25** as a pale brown oil (30 mg, 65%). ^{1}H NMR (200 MHz, CDCl3) δ 5.8–5.6 (m, 2H), 4.5–4.4 and 4.25–4.10 (m, 2H), 3.71 (s, 3H), 3.5–3.4 and 3.1–2.2 (m, 12H), 1.7–1.2 (m, 8H), 0.90 (t, $J=7$ Hz, 3H).

3-Oxa-7-thiaPGE$_1$ 26. To a stirred mixture of **25** (30 mg, 0.065 mmol) in ethanol (1 mL) and phosphate buffer (pH 7.4, 5 mL) was added PLE (0.1 mL) at room temperature. The reaction mixture was stirred vigorously for 1.5 h and the resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$. The mixture was extracted with EtOAc twice, dried over Na_2SO_4 and evaporated. Purification by column chromatography on silica gel (EtOAc/hexane, 1/1–EtOAc/hexane/AcOH, 30/10/1–EtOAc/AcOH, 40/1) provided **13** as a pale yellow oil (22 mg, 65%). IR (neat) 3369, 2930, 1741, 1403, 1225, 1132, 1077 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.5 (m, 2H), 5.0–4.4 (3H, br), 4.5–4.4 and 4.2–4.0 (m, 2H), 4.10 (s, 2H), 3.8–3.5 (m, 2H), 3.5–3.4 and 3.2–2.3 (m, 6H), 2.0–1.8 (m, 2H), 1.7–1.2 (m, 8H), 1.0–0.8 (m, 3H); MS (FAB) m/z 357 $(M-H_2O+H)^+$.

2,2-Dibutyl-[1,3,2]dioxastanninane 28. A solution of 1,3-propanedithiol **27** (6.0 g, 55.4 mmol) and dibutyltin-oxide (13.8 g, 55.4 mmol) in benzene (60 mL) was azeotropically stirred under reflux for 3 h. After the reaction was completed, the solvent was evaporated to give **28** as a white solid (18.7 g, 100%). ^{1}H NMR (200 MHz, CDCl3) δ 2.94 (t, $J=6$ Hz, 4H), 1.88 (m, 2H), 1.69 (m, 4H), 1.6–1.3 (m, 8H), 0.93 (t, $J=7$ Hz, 6H).

Methyl 6-mercapto-3-thiahexanate 29. To a solution of **28** (18.7 g, 55.4 mmol) in DMF (40 mL) was added methyl bromoacetate (7.87 mL, 83.1 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 5 h. After cooling to room temperature, the reaction mixture was treated with water and stirred for 1 h. The mixture was extracted with EtOAc and the organic layer was washed with brine, and dried over Na_2SO_4. After removal of solvents, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/20–1/9–1/4) to afford **29** as a colorless oil (5.59 g, 56%).

2-(6-Carbomethoxy-1,5-dithiahexyl)-4-(*R*)-*t*-butyldimethylsilyloxy-2-cyclopentenone 30. A solution of **8** (3.0 g, 13 mmol) and **29** (2.46 g, 13.7 mmol) in CH_2Cl_2 (45 mL) was stirred at room temperature in the presence of activated alumina (13 g). After stirring for 12 h, alumina was removed by filtration and washed with CH_2Cl_2 repeatedly. The filtrate was evaporated and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/10–1/4) to give **30** as a colorless oil (4.19 g, 83%). ^{1}H NMR (200 MHz, CDCl3) δ 6.87 (d, $J=3$ Hz, 1H), 4.96 (m, 1H), 3.75 (s, 3H), 3.23 (s, 2H), 2.96 (t, $J=7$ Hz, 2H), 2.85 (dd, $J=18$, 6 Hz, 1H), 2.77 (t, $J=7$ Hz, 2H), 2.37 (dd, $J=18$, 2 Hz, 1H), 1.98 (m, 2H), 0.91 (m, 9H), 0.13 (m, 6H).

3,7-DithiaPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31a. To a stirred solution of 3-(*S*)-*t*-butyldimethylsilyloxy-1-iodo-1-octene **10a** (368 mg, 1.0 mmol) in freshly distilled dry diethylether (4 mL) was slowly added *t*-butyllithium (1.57 M in pentane, 1.27 mL, 2.0 mmol) at −70 °C under Ar and the reaction mixture was stirred for 1 h at that temperature. To the resulting suspension was added dropwise lithium 2-thienylcyanocuprate (0.25 M in THF, 4.4 mL, 1.1 mmol) in 4 min. The gray suspension was stirred for an additional 15 min and 2-(6-carbomethoxy-1,5-dithiahexyl)-4-(*R*)-*t*-butyldimethylsilyloxy-2-cyclopentenone **30** (300 mg, 0.84 mmol) in THF (3.5 mL) was added dropwise in 8 min. The resulting yellowish mixture was allowed to warm to −20 °C over 1 h and then poured into hexane (10 mL) and saturated aqueous NH_4Cl (10 mL) with stirring. The aqueous layer was extracted with hexane and the combined organic layer was washed with saturated aqueous NH_4Cl, H_2O 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, 1/20–1/9) to afford **31a** as a pale yellow oil (342 mg, 64%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.67 (dd, $J=16$, 5 Hz, 1H), 5.53 (dd, $J=16$, 7 Hz, 1H), 4.08 (m, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 2.9–2.3 (m, 8H), 1.87 (m, 2H), 1.6–1.2 (m, 8H), 1.0–0.8 (m, 21H), 0.1–0.0 (m, 12H).

3,7-Dithia-ω-norPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31b. 64% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.4 (m, 2H), 4.2–4.0 (m, 2H), 3.73 (s, 3H), 3.21 (s, 2H), 2.9–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.6–1.2 (m, 6H), 1.0–0.8 (m, 21H), 0.1–0.0 (m, 12H).

3,7-Dithia-ω-homoPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31c. 71% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7–5.5 (m, 2H), 4.4–4.0 (m, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.45–2.8 (m, 1H), 2.9–2.3 (m, 7H), 1.95–1.75 (m, 2H), 1.6–1.1 (m, 10H), 1.0–0.8 (m, 21H), 0.1–0.0 (m, 12H).

3,7-Dithia-19-Δ-PGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31d. 71% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.6 (m, 3H), 5.1–4.8 (m, 2H), 4.4–4.05 (m, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.5–2.2 (m, 8H), 2.1–1.8 (m, 4H), 1.7–1.3 (m, 4H), 0.89 (s, 9H), 0.88 (s, 9H), 0.1–0.0 (m, 12H).

3,7-Dithia-19,20-methanoPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31e. 41% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7–5.5 (m, 2H), 4.4–4.1 (m, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.5–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.6–1.0 (m, 6H), 0.89 (s, 9H), 0.87 (s, 9H), 0.7–0.5 (m, 1H), 0.45–0.3 (m, 2H), 0.05 (s, 6H), 0.03 (s, 6H), 0.05–0.0 (m, 2H).

3,7-Dithia-16-(*S*)-methylPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31f. 64% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7–5.4 (m, 2H), 4.2–4.0 (m, 1H), 4.0–3.9 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 2.9–2.3 (m, 2H), 2.0–1.8 (m, 2H), 1.5–1.1 (m, 7H), 1.0–0.8 (m, 24H), 0.1–0.0 (m, 12H).

3,7-Dithia-16-(*R*)-methylPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31g. 72% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7–5.4 (m, 2H), 4.2–3.9 (m, 2H), 3.72 (s, 3H), 3.22 (s, 2H), 2.9–2.3 (m, 8H), 2.0–1.8 (m, 2H), 1.7–1.0 (m, 7H), 1.0–0.8 (m, 24H), 0.1–0.0 (m, 12H).

3,7-Dithia-17-(*R*)-methylPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31h. 57% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.75–5.39 (m, 2H), 4.41–4.00 (m, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.48–2.11 (m, 8H), 1.98–1.78 (m, 2H), 1.71–1.02 (m, 9H), 1.0–0.8 (m, 24H), 0.1–0.0 (m, 12H).

3,7-Dithia-17-(*S*)-methylPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31i. 56% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.67 (dd, $J=16$, 5 Hz, 1H), 5.53 (dd, $J=16$, 7 Hz, 1H), 4.4–4.0 (m, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.5–2.3 (m, 8H), 2.0–1.7 (m, 2H), 1.6–1.0 (m, 9H), 1.0–0.8 (m, 24H), 0.05 (m, 12H).

3,7-Dithia-18-methyl-ω-norPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31j. 75% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7–5.5 (m, 2H), 4.4–4.05 (m, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.5–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.6–1.4 (m, 3H), 1.3–1.1 (m, 2H), 1.0–0.8 (m, 24H), 0.1–0.0 (m, 12H).

3,7-Dithia-17-ethyl-ω-norPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31k. 64% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.4 (m, 2H), 4.25–4.00 (m, 2H), 3.73 (s, 3H), 3.21 (s, 2H), 2.9–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.5–1.2 (m, 7H), 0.90 (s, 9H), 0.88 (s, 9H), 0.83 (t, $J=7$ Hz, 6H), 0.1–0.0 (m, 12H).

3,7-Dithia-15-cyclopentyl-ω-pentanorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31l. 58% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.76–5.32 (m, 2H), 4.42–3.82 (m, 3H), 3.73 (s, 3H), 3.22 (s, 2H), 3.06–2.20 (m, 8H), 2.04–1.14 (m, 10H), 0.92–0.85 (m, 18H), 0.08–0.01 (m, 12H).

3,7-Dithia-15-cyclohexyl-ω-pentanorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31m. 32% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7–5.3 (m, 2H), 4.4–3.8 (m, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.5–2.1 (m, 8H), 2.0–1.5 (m, 7H), 1.4–0.9 (m, 6H), 0.9–0.8 (m, 18H), 0.1–0.0 (m, 12H).

3,7-Dithia-16-cyclopentyl-ω-tetranorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31n. 52% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.70 (dd, $J=15$, 5.5 Hz, 1H), 5.54 (dd, $J=15$, 7.7 Hz, 1H), 4.36 (m, 1H), 4.10 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.48–2.22 (m, 8H), 1.97–1.00 (m, 13H), 1.0–0.8 (m, 18H), 0.1–0.0 (m, 12H).

3,7-Dithia-16-cyclohexyl-ω-tetranorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31o. 52% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.76–5.36 (m, 2H), 4.42–4.00 (m, 3H), 3.74 (s, 3H), 3.22 (s, 2H), 3.06–2.10 (m, 7H), 1.98–1.06 (m, 15H), 0.92–0.85 m, 18H), 0.08–0.00 (m, 12H).

3,7-Dithia-16-phenyl-ω-tetranorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31p. 65% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.12 (m, 5H), 5.79–5.65 (m, 1H), 5.52 (dd, $J=15.7$, 8.1 Hz, 1H), 4.38–3.42 (m, 6H), 3.22 (s, 2H), 3.00–2.05 (m, 9H), 2.00–1.70 (m, 2H), 0.89 (s, 9H), 0.85 (s, 9H), 0.12–0.05 (m, 6H), 0.06 (s, 3H), 0.08 (s, 3H), 0.23 (s, 3H), 0.25 (s, 3H).

3,7-Dithia-17-phenyl-ω-trinorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31q. 62% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 5H), 5.73 (dd, $J=16$, 5 Hz, 1H), 5.55 (dd, $J=16$, 7 Hz, 1H), 4.3–4.0 (m, 2H), 3.72 (s, 3H), 3.19 (s, 2H), 2.9–2.5 (m, 9H), 2.37 (dd, $J=19$, 8 Hz, 1H), 2.0–1.7 (m, 4H), 1.0–0.8 (m, 18H), 0.2–0.0 (m, 12H).

3,7-Dithia-16-phenoxy–ω-tetranorPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 31r. 35% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.20 (m, 2H), 6.94 (t, $J=8$ Hz, 1H), 6.87 (d, $J=7$ Hz, 2H), 5.85–5.75 (m, 2H), 4.75–4.65 and 4.65–4.50 (m, 1H), 4.45–4.35 and 4.15–4.00 (m, 1H), 3.95–3.80 (m, 2H), 3.74 (s, 3H), 3.22 (S, 2H), 3.45–3.40 and 3.0–2.5 (m, 7H), 2.5–2.1 (m, 1H), 2.0–1.7 (m, 2H), 1.0–0.8 (m, 18H), 0.2–0.0 (m, 12H).

3,7-DithiaPGE$_1$ methyl ester 32a. A solution of **31a** (947 mg, 1.5 mmol) and pyridine (4.5 mL) in acetonitrile (30 mL) was cooled in an ice-bath and treated with $(HF)_n$·py (Aldrich, 9 mL). The reaction mixture was stirred for 30 min at room temperature and then slowly poured into a heterogeneous solution of EtOAc (60 mL) and saturated aqueous $NaHCO_3$ (200 mL) with stirring. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with 1 N HCl, H_2O and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/1–3/1 then EtOAc/AcOH, 100/1) to afford 3,7-dithiaPGE$_1$ methyl ester **32a** as a yellow oil (560 mg, 92%). IR (neat) 3392, 2929, 2858, 1741, 1437, 1283, 1137, 1080, 1016, 969 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85–5.55 (m, 2H), 4.5–4.4 and 4.25–4.05 (m, 2H), 3.74 (s, 3H), 3.22 (s, 2H), 3.45–3.40 and 3.05–2.20 (m, 8H), 2.0–1.8 (m, 2H), 1.6–1.2 (m, 8H), 0.89 (t, $J=7$ Hz, 3H); MS (EI) m/z 404 $(M)^+$.

3,7-Dithia-ω-norPGE$_1$ methyl ester 32b. 85% yield; IR (neat) 3401, 2930, 1740, 1437, 1282, 1138, 1079 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85—5.55 (m, 2H), 4.5–4.4 and 4.2–4.0 (m, 2H), 3.74 (s, 3H), 3.45–3.40 and 3.1–2.2 (m, 8H), 3.22 (s, 2H), 2.0–1.8 (m, 2H), 1.7–1.2 (m, 6H), 0.92 (3H, t, $J=7$ Hz); MS (EI) m/z 390 $(M)^+$.

3,7-Dithia-ω-homoPGE$_1$ methyl ester 32c. 89% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.75–5.55 (m, 2H), 4.5–4.1 (m, 2H), 3.74 (s, 3H), 3.23 (s, 2H), 3.4–2.2 (m, 8H), 2.0–1.2 (m, 12H), 0.89 (t, $J=6$ Hz, 3H); MS (FAB) m/z 401 $(M-H_2O+H)^+$.

3,7-Dithia-19-Δ-PGE$_1$ methyl ester 32d. 78% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85–5.6 (m, 3H), 5.1–4.9 (m, 2H), 4.5–4.1 (m, 2H), 3.74 (s, 3H), 3.23 (s, 2H), 3.4–2.2 (m, 8H), 2.2–2.0 (m, 2H), 1.95–1.85 (m, 2H), 1.6–1.4 (m, 4H); MS (EI) m/z 402 $(M)^+$.

3,7-Dithia-19,20-methanoPGE$_1$ methyl ester 32e. 67% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.6 (m, 2H), 4.45–4.1 (m, 2H), 3.73 (s, 3H), 3.21 (s, 2H), 3.4–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.6–1.4 (m, 4H), 1.25–1.15 (m, 2H), 0.7–0.6 (m, 1H), 0.5–0.3 (m, 2H), 0.05–0.0 (m, 2H); MS (EI) m/z 416 $(M)^+$.

3,7-Dithia-16-(*S*)-methylPGE$_1$ methyl ester 32f. 72% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9–5.5 (m, 2H), 4.5–4.4 and 4.1–4.0 (m, 1H), 4.3–4.1 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.5–3.4 and 3.1–2.3 (m, 10H), 2.0–1.8 (m, 2H), 1.6–1.0 (m, 7H), 1.0–0.8 (m, 6H).

3,7-Dithia-16-(*R*)-methylPGE$_1$ methyl ester 32g. 82% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.5 (m, 2H), 4.5–4.4 and 4.2–4.0 (m, 2H), 3.73 (s, 3H), 3.23 (s, 2H), 3.5–3.4 and 3.1–2.3 (m, 8H), 2.0–1.8 (m, 2H), 1.7–1.2 (m, 7H), 1.0–0.8 (m, 6H).

3,7-Dithia-17-(*R*)-methylPGE$_1$ methyl ester 32h. 64% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.76 (1H, dd, J = 16, 6 Hz), 5.61 (1H, dd, J = 16, 8 Hz), 4.4–4.1 (m, 2H), 3.74 (s, 3H), 3.23 (s, 2H), 3.42–2.17 (m, 8H), 1.88 (m, 2H), 1.58 (m, 2H), 1.23 (m, 7H), 0.91 (m, 6H); MS (FAB) m/z; 415 $(M-H_2O+H)^+$.

3,7-Dithia-17-(*S*)-methylPGE$_1$ methyl ester 32i. 88% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.70 (m, 2H), 4.5–4.1 (m, 2H), 3.74 (s, 3H), 3.23 (s, 2H), 3.4–2.2 (m, 8H), 2.0–1.0 (m, 11H), 1.0–0.8 (m, 6H); MS (FAB) m/z; 432 $(M)^+$.

3,7-Dithia-18-methyl-ω-norPGE$_1$ methyl ester 32j. 79% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.6 (m, 2H), 4.5–4.1 (m, 2H), 3.74 (s, 3H), 3.23 (s, 2H), 3.4–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.6–1.4 (m, 3H), 1.3–1.1 (m, 2H), 0.90 (d, J = 7 Hz, 6H).

3,7-Dithia-17-ethyl-ω-norPGE$_1$ methyl ester 32k. 79% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85–5.55 (m, 2H), 4.5–4.4 and 4.3–4.1 (m, 2H), 3.77 (s, 3H), 3.24 (s, 2H), 3.45—3.40 and 3.1–2.2 (m, 8H), 2.0–1.2 (m, 9H), 0.89 (t, J = 7 Hz, 6H).

3,7-Dithia-15-cyclopentyl-ω-pentanorPGE$_1$ methyl ester 32l. 58% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.88–5.48 (m, 2H), 4.56–3.84 (m, 3H), 3.72 (s, 3H), 3.20 (s, 2H), 3.14–2.20 (m, 9H), 2.20–1.10 (m, 9H); MS (FAB) m/z 385 $(M-H_2O+H)^+$.

3,7-Dithia-15-cyclohexyl-ω-pentanorPGE$_1$ methyl ester 32m. 67% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.74 (dd, J = 15, 7 Hz, 1H,), 5.56 (dd, J = 15, 8 Hz, 1H), 4.4–3.8 (m, 2H), 3.74 (s, 3H), 3.22 (s, 2H), 3.4–2.1 (m, 8H), 2.0–1.5 (m, 7H), 1.5–0.8 (m, 6H); MS (FAB) m/z 399 $(M-H_2O+H)^+$.

3,7-Dithia-16-cyclopentyl-ω-tetranorPGE$_1$ methyl ester 32n. 84% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.6 (m, 2H), 4.43 (m, 1H), 4.15 (m, 1H), 3.74 (s, 3H), 3.23 (s, 2H), 3.42–2.17 (m, 8H), 2.00–1.40 (m, 11H), 1.2–1.0 (m, 2H).

3,7-Dithia-16-cyclohexyl-ω-tetranorPGE$_1$ methyl ester 32o. 63% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.80–5.40 (m, 2H), 4.48–3.94 (m, 3H), 3.71 (s, 3H), 3.20 (s, 2H), 3.10–2.10 (m, 9H), 2.00–1.54 (m, 6H), 1.54–0.76 (m, 8H).

3,7-Dithia-16-phenyl-ω-tetranorPGE$_1$ methyl ester 32p. 79% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.15 (m, 5H), 5.78 (dd, J = 15.4, 5.8 Hz, 1H), 5.56 (dd, J = 15.4, 8.0 Hz, 1H), 4.46–4.28 (m, 2H), 4.12–3.94 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.06–2.14 (m, 9H), 2.00–1.70 (m, 2H).

3,7-Dithia-17-phenyl-ω-trinorPGE$_1$ methyl ester 32q. 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H), 5.85–5.55 (m, 2H), 4.5–4.4 and 4.2–4.0 (m, 2H), 3.72 (s, 3H), 3.00 (s, 2H), 3.45–3.40 and 3.05–2.20 (m, 10H), 2.0–1.8 (m, 4H).

3,7-Dithia-16-phenoxy-ω-tetranorPGE$_1$ methyl ester 32r. 61% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.1 (m, 2H), 6.98 (t, J = 8 Hz, 1H), 6.92 (d, J = 7 Hz, 2H), 5.9–5.8 (m, 2H), 4.6–4.5 (m, 1H), 4.5–4.4 and 4.2–4.1 (m, 1H), 4.07 and 4.05 (d, J = 9 Hz, 1H), 3.95 and 3.91 (d, J = 9 Hz, 1H), 3.74 (s, 3H), 3.21 (S, 2H), 3.4–3.3 and 3.1–2.3 (m, 8H), 2.0–1.8 (m, 2H).

3,7-DithiaPGE$_1$ 4a. To a stirred mixture of **32a** (370 mg, 0.91 mmol) in ethanol (5 mL) and phophate buffer (pH 7.4, 25 mL) was added PLE (0.5 mL) at room temperature. The reaction mixture was stirred for 1 h. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ and then extracted with EtOAc twice. The combined organic layer was dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica gel (EtOAc/hexane, 3/1 to EtOAc/AcOH, 50/1) provided **4a** as a pale yellow oil (372 mg, 92%). IR (neat) 3392, 2929, 2858, 1733, 1417, 1262, 1135, 1077, 969 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9–5.6 (m, 2H), 5.2–4.5 (br, 3H), 4.5–4.4 and 4.3–4.1 (m, 2H), 3.22 (s, 2H), 3.45–3.40 and 3.1–2.3 (m, 8H), 2.0–1.8 (m, 2H), 1.7–1.5 (m, 2H), 1.5–1.2 (m, 6H), 0.92 (t, J = 7 Hz, 3H); MS (EI) m/z 372 $(M-H_2O)^+$.

3,7-Dithia-ω-norPGE$_1$ 4b. 85% yield; IR (neat) 3382, 2928, 1733, 1417, 1262, 1134, 1077, 970, 909, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85–5.60 (m, 2H), 5.6–5.2 (3H, br), 4.5–4.4 and 4.25–4.05 (m, 2H), 3.23 (s, 2H), 3.45–3.40 and 3.1–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.7–1.2 (m, 6H), 0.92 (3H, t, J = 7 Hz); MS (EI) m/z 358 $(M-H_2O)^+$.

3,7-Dithia-ω-homoPGE$_1$ 4c. 70% yield; IR (neat) 3368, 2927, 2857, 2654, 1732, 1417, 1345, 1262, 1137, 1078, 969, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.6 (m, 2H), 5.6–5.2 (br), 4.5–4.1 (m, 2H), 3.4–3.0 (m, 1H), 3.23 (s, 2H), 3.0–2.2 (m, 7H), 1.95–1.75 (m, 2H), 1.65–

1.5 (m, 2H), 1.5–1.2 (m, 8H), 0.89 (t, $J=6$ Hz, 3H); MS (APCI) m/z 403 $(M-H)^-$.

3,7-Dithia-19-Δ-PGE$_1$ 4d. 69% yield; IR (neat) 3392, 2928, 2649, 1733, 1640, 1417, 1262, 1148, 1078, 970, 914 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9–5.5 (m, 3H), 5.1–4.9 (m, 2H), 4.45–4.1 (m, 2H), 3.4–3.0 (m, 1H), 3.22 (s, 2H), 3.0–2.3 (m, 7H), 2.2–2.0 (m, 2H), 1.95–1.85 (m, 2H), 1.65–1.35 (m, 4H); MS (APCI) m/z 387 $(M-H)^-$.

3,7-Dithia-19,20-methanoPGE$_1$ 4e. 84% yield; IR (neat) 3392, 3076, 2998, 2927, 2857, 2653, 1732, 1417, 1265, 1148, 1078, 970 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.6 (m, 2H), 4.5–4.1 (m, 2H), 3.4–3.0 (m, 1H), 3.23 (s, 2H), 3.0–2.2 (m, 7H), 2.0–1.8 (m, 2H), 1.7–1.1 (m, 6H), 0.7–0.6 (m, 1H), 0.5–0.3 (m, 2H), 0.05–0.0 (m, 1H); MS (APCI) m/z 401 $(M-H)^-$.

3,7-Dithia-16-(*S*)-methylPGE$_1$ 4f. 89% yield; IR (neat) 3368, 2926, 1733, 1417, 1262, 1148, 1078, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85–5.60 (m, 2H), 4.5–4.4 and 4.2–4.0 (m, 2H), 4.6–3.8 (br, 3H), 3.22 (s, 2H), 3.45–3.40 and 3.1–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.7–1.1 (m, 7H), 1.0–0.8 (m, 6H); MS (EI) m/z 386 $(M-H_2O)^+$.

3,7-Dithia-16-(*R*)-methylPGE$_1$ 4g. 72% yield; IR (neat) 3401, 2928, 1730, 1417, 1262, 1147, 1078, 971, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9–5.6 (m, 2H), 4.5–4.4 and 4.3–4.0 (m, 2H), 4.7–3.9 (br, 3H), 3.23 (s, 2H), 3.45–3.40 and 2.9–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.7–1.0 (m, 7H), 1.0–0.8 (m, 6H); MS (EI) m/z 386 $(M-H_2O)^+$.

3,7-Dithia-17-(*R*)-methylPGE$_1$ 4h. yield; IR (neat) 3392, 2955, 2926, 2872, 2858, 2648, 1732, 1715, 1417, 1383, 1271, 1151, 1080, 970 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85–5.65 (m, 2H), 5.2–5.0 (3H, br), 4.5–4.05 (m, 2H), 3.4–2.2 (m, 8H), 3.23 (s, 2H), 2.0–1.8 (m, 2H), 1.60–1.02 (m, 9H), 1.0–0.8 (m, 6H); MS (EI) m/z 400 $(M-H_2O)^+$.

3,7-Dithia-17-(*S*)-methylPGE$_1$ 4i. yield; IR (neat) 3392, 2927, 2872, 1730, 1715, 1404, 1265, 1151, 1079, 969, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.74 (dd, $J=15$, 6 Hz, 1H), 5.67 (dd, $J=15$, 8 Hz, 1H), 4.9–4.6 (br), 4.5–4.15 (m, 2H), 3.4–2.2 (m, 8H), 3.23 (s, 2H), 2.0–1.75 (m, 2H), 1.6–1.0 (m, 9H), 1.0–0.8 (m, 6H); MS (APCI) m/z 417 $(M-H)^-$.

3,7-Dithia-18-methyl-ω-norPGE$_1$ 4j. 92% yield; IR (neat) 3392, 2954, 2869, 1732, 1417, 1385, 1262, 1147, 1077, 970 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8–5.6 (m, 3H), 4.5–4.1 (m, 2H), 3.4–3.0 (m, 1H), 3.23 (s, 2H), 3.0–2.2 (m, 7H), 2.0–1.8 (m, 2H), 1.7–1.5 (m, 3H), 1.3–1.1 (m, 2H), 0.90 (d, $J=7$ Hz, 6H); MS (APCI) m/z 389 $(M-H)^-$.

3,7-Dithia-17-ethyl-ω-norPGE$_1$ 4k. 59% yield; IR (neat) 3392, 2964, 2927, 1731, 1417, 1263, 1148, 1077, 972 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9–5.6 (m, 2H), 5.6–5.0 (3H, br), 4.6–4.0 (m, 2H), 3.23 (s, 2H), 3.45–3.40 and 3.1–2.2 (m, 8H), 2.0–1.8 (m, 2H), 1.6–1.2 (m, 7H), 0.83 (6H, t, $J=7$ Hz); MS (EI) m/z 386 $(M-H_2O)^+$.

3,7-Dithia-15-cyclopentyl-ω-pentanorPGE$_1$ 4l. 25% yield; IR (neat) 3700–3100, 2926, 2856, 1739, 1403, 1385, 1261, 1153, 1076, 1024, 801, 734 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.86–5.48 (m, 2H), 4.70–3.20 (m, 6H), 3.15 (s, 2H), 3.08–1.00 (m, 18H); MS (APCI) m/z 387 $(M-H)^-$.

3,7-Dithia-15-cyclohexyl-ω-pentanorPGE$_1$ 4m. 72% yield; IR (neat) 3392, 2956, 2926, 2872, 1733, 1715, 1417, 1381, 1271, 1144, 1080, 970 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.77 (dd, $J=15$, 6 Hz, 1H), 5.61 (dd, $J=15$, 8 Hz, 1H), 4.85–4.65 (br, 3H), 4.5–4.1 (m, 1H), 3.92 (m, 1H), 3.4–2.3 (m, 8H), 3.23 (s, 2H), 2.0–1.6 (m, 7H), 1.5–0.9 (m, 6H); MS (APCI) m/z 401 $(M-H)^-$.

3,7-Dithia-16-cyclopentyl-ω-tetranorPGE$_1$ 4n. 89% yield; IR (neat) 3392, 2947, 2867, 2649, 1731, 1715, 1417, 1265, 1148, 1078, 971 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9–5.6 (m, 5H), 4.44 (m, 1H), 4.18 (m, 1H), 3.42–3.03 (m, 1H), 3.23 (s, 2H), 2.96–2.20 (m, 7H), 2.01–1.38 (m, 11H), 1.2–1.0 (m, 2H); MS (EI) m/z 384 $(M-H_2O)^+$.

3,7-Dithia-16-cyclohexyl-ω-tetranorPGE$_1$ 4o. 34% yield; IR (neat) 3600–3100, 2922, 2852, 1732, 1448, 1417, 1261, 1142, 973, 897, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.90–5.52 (m, 2H), 5.04–4.40 (br), 4.40–3.92 (m, 3H), 3.22 (s, 2H), 3.12–2.24 (m, 7H), 2.24–0.70 (m, 15H); MS (FAB) m/z 399 $(M-H_2O+H)^+$.

3,7-Dithia-16-phenyl-ω-tetranorPGE$_1$ 4p. 28% yield; IR (neat) 3700–3100, 2921, 2856, 1732, 1495, 1455, 1407, 1266, 1148, 1080, 1029, 911, 735, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.16 (m, 5H), 5.90–5.50 (m, 2H), 4.56–3.70 (m, 7H), 3.21 (s, 2H), 3.10–2.26 (m, 10H), 2.0–1.8 (m, 2H); MS (MALDI) m/z 449 $(M+K)^+$, 433 $(M+Na)^+$.

3,7-Dithia-17-phenyl-ω-trinorPGE$_1$ 4q. 72% yield; IR (neat) 3392, 2923, 1730, 1406, 1264, 1152, 1076, 911, 734, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H), 5.9–5.6 (m, 2H), 4.5–4.4 and 4.3–4.0 (m, 2H), 4.3–3.6 (br, 3H), 3.03 (s, 2H), 3.45–3.40 and 3.05–2.20 (m, 10H), 2.0–1.8 (m, 4H); MS (EI) m/z 406 $(M-H_2O)^+$.

3,7-Dithia-16-phenoxy-ω-tetranorPGE$_1$ 4r. 58% yield; IR (neat) 3392, 2925, 1730, 1599, 1495, 1406, 1245, 1147, 1080, 1040, 972, 908, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (t, $J=8$ Hz, 2H), 6.98 (t, $J=8$ Hz, 1H), 6.92 (d, $J=8$ Hz, 2H), 6.0–5.8 (m, 2H), 4.7–4.6 (m, 1H), 4.6–4.4 and 4.2–3.9 (m, 3H), 4.7–3.7 (br, 3H), 3.22 (S, 2H), 3.45–3.40 and 3.1–2.3 (m, 8H), 2.0–1.8 (m, 2H); MS (FAB) m/z 427 $(M-H_2O)^+$.

3,7-Dithia-13,14-dihydroPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 34a. To a stirred solution of 3-(*S*)-*t*-butyldimethylsilyloxy-1-iodo-1-octene **33a** (90 mg, 0.243 mmol) in freshly distilled dry ether (0.5 mL) was slowly added *t*-butyllithium (1.57 M in pentane, 0.31 mL, 0.49 mmol) at −70 °C under Ar and the reaction mixture was stirred for 1 h at that temperature. To

the resulting suspension was added dropwise lithium 2-thienylcyanocuprate (0.25 M in THF, 1.0 mL, 0.25 mmol) in 4 min. The gray suspension was stirred for an additional 15 min and 2-(6-carbomethoxy-1,5-dithiahexyl)-4-(*R*)-*t*-butyldimethylsilyloxy-2-cyclopentenone **30** (73 mg, 0.19 mmol) in THF (3 mL) was added dropwise in 4 min. The resulting yellowish mixture was allowed to warm to −20 °C over 1 h and then poured into a stirred mixture of hexane (10 mL) and saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with hexane and the combined organic layer was successively washed with saturated aqueous NH_4Cl, H_2O, 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, 1/20–1/9) to afford **34a** as a pale yellow oil (81 mg, 53%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.25–4.15 (m, 1H), 4.05–3.95 (m, 1H), 3.74 (s, 3H), 3.7–3.6 (m, 1H), 3.23 (s, 2H), 3.3–2.3 (m, 7H), 2.0–1.0 (m, 15H), 1.0–0.8 (m, 21H), 0.1–0.0 (m, 12H).

3,7-Dithia-15-Me-PGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 34b. 65% yield; ^{1}H NMR (200 MHz, CDCl3) δ 5.69 (d, J = 15.4 Hz, 1H), 5.5–5.4 (m, 1H), 4.44–4.30 (m, 1H), 4.15–3.98 (m, 1H), 3.74 (s, 3H), 3.21 (s, 2H), 3.00–2.10 (m, 8H), 2.00–1.76 (m, 2H), 1.60–1.14 (m, 11H), 0.93–0.82 (m, 12H), 0.11 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

3,7-Dithia-15-deoxy-16-(*S*)-hydroxy-16-methylPGE$_1$ methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) 34c. 34% yield; ^{1}H NMR (200 MHz, CDCl3) δ 5.67 (dt, J = 16, 7 Hz, 1H), 5.34 (dd, J = 16, 8 Hz, 1H), 4.04 (q, J = 7 Hz, 1H), 3.73 (s, 3H), 3.20 (S, 2H), 2.9–2.2 (m, 10H), 2.0–1.8 (m, 2H), 1.5–1.2 (m, 9H), 1.0–0.8 (m, 12H), 0.2–0.0 (m, 12H).

3,7-Dithia-13,14-dihydroPGE$_1$ methyl ester 35a. A solution of bis(*t*-butyldimethylsilyl ether) **34a** (68 mg, 0.11 mmol) and pyridine (0.4 mL) in CH_3CN (2.5 mL) was cooled in an ice-bath and treated with $(HF)_n$·py (Aldrich, 0.8 mL). The reaction mixture was stirred for 30 min at room temperature and then slowly poured into a stirred mixture of EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc twice and the combined EtOAc layer was successively washed with 1 N HCl, H_2O, 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, 1/1–3/1 then EtOAc/AcOH, 100/1) to afford **35a** as a yellow oil (37 mg, 84%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.4–4.3 (m, 1H), 4.2–4.1 (m, 1H), 3.75 (s, 3H), 3.7–3.6 (m, 1H), 3.24 (s, 2H), 3.4–2.4 (m, 7H), 2.3–2.2 (m, 1H), 2.1–1.1 (m, 14H), 0.90 (t, J = 6 Hz, 3H).

3,7-Dithia-15-Me-PGE$_1$ methyl ester 35b. 48% yield; ^{1}H NMR (200 MHz, CDCl3) δ 5.78 (d, J = 15.4 Hz, 1H), 5.7–5.5 (m, 1H), 4.49–4.34 (m, 1H), 4.20–4.02 (m, 1H), 3.72 (s, 3H), 3.21 (s, 2H), 3.06–2.00 (m, 9H), 2.00–1.86 (m, 2H), 1.60–1.44 (m, 2H), 1.40–1.18 (m, 9H), 0.87 (t, J = 6.5 Hz, 3H).

3,7-Dithia–15-deoxy-16-(*S*)-hydroxy-16-methylPGE$_1$ methyl ester 35c. 66% yield; ^{1}H NMR (200 MHz, CDCl3) δ 5.85–5.70 (m, 1H), 5.6–5.4 (m, 1H), 4.5–4.4 and 4.2–4.0 (m, 1H), 3.74 (s, 3H), 3.22 (s, 2H), 3.5–3.4 and 3.0–2.2 (m, 12H), 2.0–1.8 (m, 2H), 1.6–1.1 (m, 9H), 0.92 (t, J = 7 Hz, 3H).

3,7-Dithia-13,14-dihydroPGE$_1$ 36a. To a stirred mixture of **32a** (30 mg, 0.074 mmol) in ethanol (0.4 mL) and phosphate buffer (pH 7.4, 4.0 mL) was added PLE (0.1 mL) at room temperature. The reaction mixture was stirred for 1 h. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ and extracted with EtOAc twice. The combined organic layer was dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica gel (EtOAc/hexane, 3/1 to EtOAc/AcOH, 50/1) provided **36a** as a pale yellow oil (18 mg, 64%). IR (neat) 3418, 2928, 2858, 2649, 1731, 1455, 1417, 1266, 1186, 1143, 1076, 911 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.4–5.1 (br), 4.4–4.3 (m, 1H), 4.2–4.1 (m, 1H), 3.75–3.7 (m, 1H), 3.23 (s, 2H), 3.4–2.4 (m, 7H), 2.3–2.2 (m, 1H), 2.1–1.1 (m, 14H), 0.90 (t, J = 6 Hz, 3H); MS (APCI) m/z 391 $(M-H)^-$.

3,7-Dithia-15-Me-PGE$_1$ 36b. 39% yield; IR (neat) 3600–3100, 2931, 2861, 1732, 1417, 1381, 1262, 1127, 1082, 974, 918, 758, 667 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.84–5.46 (m, 2H), 5.36–4.70 (br), 4.47–3.98 (m, 2H), 3.15 (s, 2H), 3.06–2.20 (m, 7H), 2.04–1.72 (m, 2H), 1.60–1.40 (m, 2H), 1.32–1.10 (m, 9H), 0.81 (t, J = 6.4 Hz, 3H); MS (FAB) m/z: 387 $(M-H_2O+H)^+$.

3,7-Dithia-15-deoxy-16-(*S*)-hydroxy-16-methylPGE$_1$ 36c. 75% yield; IR (neat) 3392, 2932, 1714, 1403, 1262, 1147, 1079, 974, 908, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9–5.7 (m, 1H), 5.7–5.5 (m, 1H), 4.6–4.4 and 4.2–4.0 (m, 1H), 4.1–3.7 (br) 3.24 (s, 2H), 3.5–3.4 and 3.2–2.2 (m, 10H), 2.0–1.8 (m, 2H), 1.6–1.1 (m, 9H), 0.93 (t, J = 7 Hz, 3H); MS (FAB) m/z 405 $(M-H_2O+H)^+$.

Prostanoid EP and IP receptor binding assay

Membranes from CHO cells expressing the 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 6 mL 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- or IP-receptors were cultured in 24-well plates (1×10^5 cells/well). After 2 days, the media were removed and cells were washed with 500 μL of Minimum Essential Medium (MEM) and preincubated for 10 min in 450 μL of assay buffer (MEM containing 1 mM of IBMX, 1% of BSA) at 37 °C. Then 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. The cAMP production was measured by radioimmunoassay using a cAMP assay kit (Amersham).

Measurement of intracellular Ca^{2+} production

Intracellular Ca^{2+} concentration was measured using Jasco CAM220 Spectrofluorometer. CHO cells expressing EP3-receptor were cultured for 2 days. After the media were 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 the 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 under stirring. Intracellular Ca^{2+} production was calculated from the ratio of the fluorescence intensities at 340 and 380 nm.

References and Notes

1. Coleman, R. A.; Smith, W. L.; Narumiya, S. *Pharmacol. Rev*. **1994**, *46*, 205.
2. Coleman, R. A.; Grix, S. P.; Head, S. A.; Louttit, J. B.; Mallett, A.; Sheldrick, R. L. G. *Prostaglandins* **1994**, *47*, 152.
3. Narumiya, S.; Sugimoto, Y.; Ushikubi, F. *Physiol. Rev*. **1999**, *79*, 1193.
4. Tanaka, T.; Okamura, N.; Bannai, K.; Hazato, A.; Sugiura, S.; Manabe, K.; Kamimoto, F.; Kurozumi, S. *Chem. Pharm. Bull*. **1985**, *33*, 2359.
5. Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem*. **1988**, *53*, 5590.
6. The enone **16** was obtained commercially from Nissan Chemical Industries, Co, Ltd.
7. Kitano, Y.; Matsumoto, T.; Wakasa, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F.; Miyaji, K.; Arai, K. *Tetrahedron Lett*. **1987**, *28*, 6351 The optical purity of the obtained allyl alcohols was >95% ee by ^{1}H NMR analysis of (*R*)- and (*S*)-MTPA ester.
8. Kiriyama, M.; Ushikubi, F.; Kobayashi, T.; Hirata, M.; Sugimoto, Y.; Narumiya, S. *Br. J. Pharmacol*. **1997**, *122*, 217.
9. The detailed biological profiles of 3-thiaPGE_1 will be reported in the following paper.
10. 16-(*R*)- and 16-(*S*)-Methyl-PGE_2 was reported to exhibit more potent inhibitory activity against gastric juice excretion than PGE_2 Hayashi, M.; Miyake, H.; Tanouchi, T.; Iguchi, S.; Iguchi, Y.; Tanouchi, F. *J. Org. Chem*. **1973**, *38*, 1250.
11. (a) 17-(*S*)-Methyl moiety was used as the ω chain moiety of Limaprost and Ornoprostil. *Drugs Future* **1982**, *7*, 116. (b) *Drugs Future* **1978**, *3*, 536.
12. (a) 15-Cyclopentyl and 15-cyclohexyl derivatives were reported to exhibit potent inhibitory activity against platelet aggregation Morley, J.; Page, C. P.; Paul, W.; Mongelli, N.; Cesarini, R.; Gandorlfi, C. *Prostaglandins, Leukotrienes, Med.* **1983**, *11*, 391. (b) ref 4. (c) Caldwell, A. G.; Harris, C. J.; Stepney, R.; Whittaker, N. J. *Chem. Soc., Perkin Trans. 1*, **1980**, 495.
13. 13,14-Dihydro-16-phenyl-ω-tetranor-PGE_2 was reported to display a tissue-selective hypotensive profile: Johnson, M. R.; Schaaf, T. K.; Constantine, J. W.; Hess, H.-J. *Prostaglandins* **1980**, *20*, 515.
14. 17-Phehyl-ω-trinor-PGE_2 was often used as a selective EP1- and/or EP3-receptor agonist in the biological evaluation. Miller, W. L.; Weeks, J. R.; Lauderdale, J. W.; Kirton, K. T. *Prostaglandins* **1975**, *9*, 9.
15. A 16-phenoxy moiety was used as the ω chain moiety of Sulprostone. *Drugs Future* **1978**, *3*, 59.
16. A 16(*R*)-methyl-16(*S*)-hydroxy-15-deoxy moiety was used as the ω chain moiety of Misoprostol. Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem*. **1983**, *26*, 786.
17. Subtype selectivity of **4p** (EC_{50}EP3/EC_{50}EP4) was reconfirmed by measuring both of the EP3- and EP4-receptor agonist activities because of its interesting biological profile as a new chemical lead.