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Design and Synthesis of a Selective EP4-Receptor Agonist. Part 2: 3,7-DithiaPGE$_1$ Derivatives with High Selectivity

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Abstract—To identify new highly selective EP4-agonists, further modification of the 16-phenyl moiety of **1** was continued. 16-(3-Methoxymethyl)phenyl derivatives **13-$_{6q}$** and 16-(3-ethoxymethyl)phenyl derivatives **13-$_{7e}$** showed more selectivity and potent agonist activity than **1**. 16-(3-Methyl-4-hydroxy)phenyl derivative **18-$_{14e}$** demonstrated excellent subtype selectivity, while both its receptor affinity and agonist activity were less potent than those of **13-$_{6q}$**. Structure–activity relationships (SARs) are also discussed.

Introduction

With chemical modification to find highly selective EP4-receptor agonists, a tremendous amount of the reported structural information[1] should be organized in advance because of the diversity of chemical modification of the PG skeleton. First, a series of 3,7-dithiaPGE$_1$ analogues were discovered in our laboratory as chemical leads for structurally new EP4-receptor agonists.[2] Second, we focused on chemical modification of their ω-chains. In our preceding paper, we reported identification of 16-phenyl-ω-tetranor-3,7-dithiaPGE$_1$ **1** derivatives as new chemical leads for EP4-receptor agonists. Since one of the important aims of this project was to identify a highly selective EP4-receptor agonist to disclose novel biological roles of the EP4-receptor, the receptor selectivity and agonist activity of **1** should be much more improved. In this study, we focused our attention on further improvement of the biological properties in **1** by chemical modification of its 16-phenyl moiety (Scheme 1). We describe here the successful modification of **1** to obtain highly selective EP4-receptor agonists **13-$_{6q}$**, **18-$_{14e}$** and others. Structure–activity relationships (SARs) are also discussed.

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Chemistry

Syntheses of 16-substituted-phenyl-ω-tetranor-3,7-dithia PGE$_1$ analogues are outlined in Scheme 2. To obtain a variety of analogues, one of the best synthetic methods included Nozaki–Hiyama coupling reaction[3] as a key step. Conjugate addition[4] of (2-tributyltin)vinylcyanocuprate, which was prepared from **3**, to the chiral enone **2** followed by trapping of the resulting enolate anion with acetic anhydride afforded the enol acetate **4**. The vinyltin part in **4** was converted to the iodoolefin **5** by treatment with iodine. Hiyama-coupling of the iodoolefin **5** and arylacetaldehyde **6a–q**, **7a–k** and **8a–m** provided **11–$_{6a}$–11–$_{8m}$**, respectively. Deprotection of the TBS groups afforded **12-$_{6a}$–12-$_{8m}$** as a diastereomeric mixture, which was separated by Lobar column to give two diastereoisomers. Compounds **13-$_{6a}$–13-$_{8m}$** derived from the corresponding more polar isomers always exhibited more potent activities than those derived from the less polar isomers. Based on this finding, the configuration of 15-OH of the more polar isomer was tentatively assigned to the natural configuration.[5] Sequential enzymatic hydrolysis of 15(*S*) **12-$_{6a}$–12-$_{8m}$**: hydrolysis of the enol ester with AmanoPS followed by hydrolysis of the methyl ester with PLE afforded **13-$_{6a}$–13-$_{8m}$**, respectively.

Synthesis of 3,7-dithiaPGE$_1$ analogues possessing miscellaneous ω chains are described in Scheme 3. According to the same procedure as described in Scheme 2,

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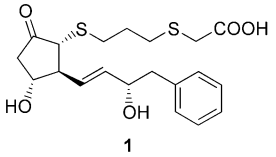
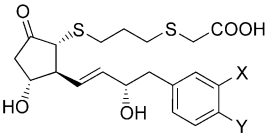
16-$_{14a}$–16-$_{15e}$, which were prepared by Hiyama-coupling reaction of **5** and miscellaneous aldehydes **14a–k** and **15a–e**, were converted to **18-$_{14a}$–18-$_{15e}$**, respectively.



1

	Ki (nM)
mEP1	2600
mEP2	3900
mEP3	130
mEP4	7.0
hIP	>10^4



13-$_{6q}$ X = CH_2OMe, Y = H

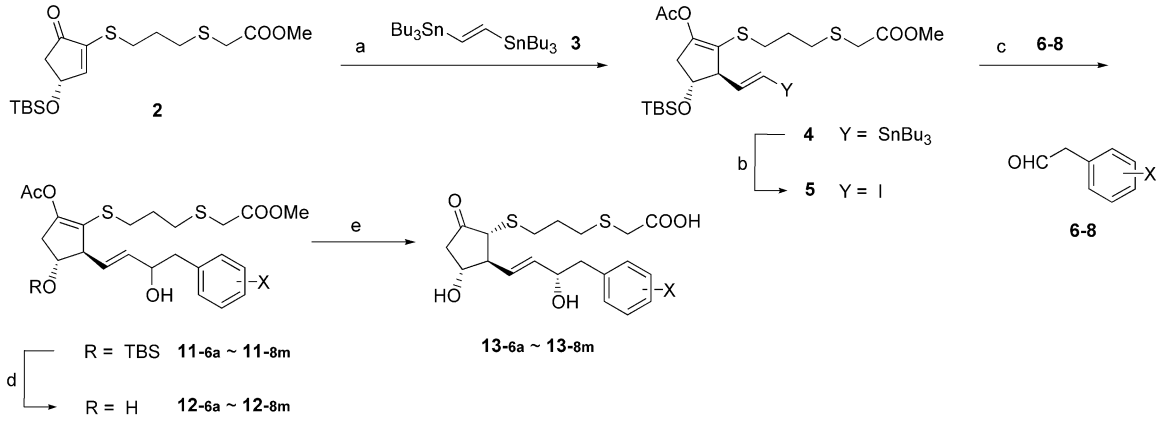
18-$_{14e}$ X = Me, Y = OH

Scheme 1. Optimization of 16-phenyl-ω-tetranor-3,7-dithia PGE_1 analogues **13-$_{6q}$** and **18-$_{14e}$**.

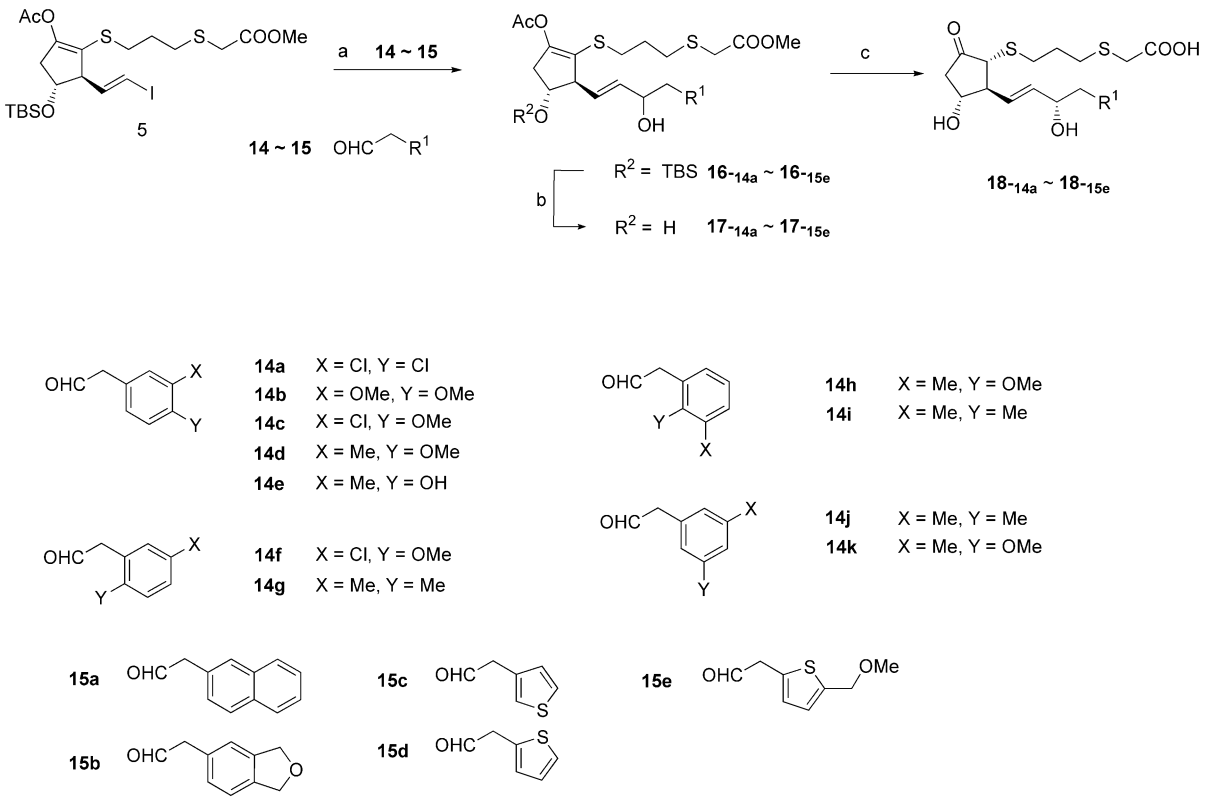
Results and Discussion

To improve the biological profiles of **1** (Scheme 1) as an EP4-receptor selective agonist, chemical modification was further continued. It was especially important to improve K_iEP4/K_iEP3 subtype selectivity because removal of the uterine contractile activity, which is mediated by EP3-receptor, is indispensable to develop EP4-receptor agonists as clinically useful drugs. Improvement of the EP4-receptor selectivity and agonist activity by introduction of substituents into the phenyl moiety of **1** was investigated. Among the compounds tested, two series of 3,7-dithiaPGE_1 analogues possessing 16-(3-alkoxymethyl)phenyl and 16-(3,4-disubstituted)phenyl analogues were found to be highly selective EP4-receptor agonists. 3,7-DithiaPGE_1 analogues possessing other miscellaneous ω-chains as described in Table 4 were also synthesized and evaluated for their ability to improve the EP4-receptor selectivity and agonist activity. 16-Thienyl-ω-tetranor-PGE_1 analogues **18-$_{15c–e}$** exhibited potent agonist activity among these analogues but their subtype selectivities were relatively low.

As described in Table 1, the effects of substituents of the phenyl moiety in **1** on the EP4-receptor selectivity and

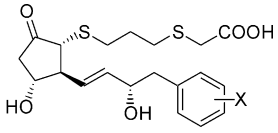


Scheme 2. Synthesis of 16-phenyl-ω-tetranor-3,7-dithia PGEs **13-$_{6a}$–13-$_{8m}$**. Reagents: (a) MeLi, CuCN, THF then Ac_2O; (b) I_2, ether; (c) $CrCl_2$, $NiCl_2$, DMF; (d) $(HF)_n$-py, pyridine, CH_3CN; (e) AmanoPS, DMSO, phosphate buffer then PLE.



Scheme 3. Synthesis of 3,7-dithiaPGs possessing miscellaneous ω chains. Reagents: (a) $CrCl_2$, $NiCl_2$, DMF; (b) $(HF)_n$•py, pyridine CH3CN; (c) AmanoPS, DMSO, phosphate buffer then PLE.

Table 1. Further optimization of 16-phenylω-tetranor-3,7-dithia PGE_1 analogues **13-$_{6a}$**–**13-$_{6r}$**



Compound	R	Binding K_i (nM)					EC_{50} (nM)
		mEP1	mEP2	mEP3	mEP4	hIP	mEP4
13-$_{6a}$	*o*-Me	$>10^4$	2500	140	22	$>10^4$	420
13-$_{6b}$	*m*-Me	$>10^4$	760	100	1.9	$>10^4$	2.8
13-$_{6c}$	*p*-Me	$>10^4$	1200	72	7.3	$>10^4$	270
13-$_{6d}$	*m*-Cl	630	2300	21	0.8	$>10^4$	1.7
13-$_{6e}$	*p*-Cl	560	240	10	5.5	$>10^4$	95
13-$_{6f}$	*o*-OMe	$>10^4$	2600	1100	32	$>10^4$	580
13-$_{6g}$	*m*-OMe	$>10^4$	$>10^4$	510	9.9	$>10^4$	37
13-$_{6h}$	*p*-OMe	3100	1500	220	7.1	$>10^4$	32
13-$_{6i}$	*m*-OEt	$>10^4$	1700	1500	30	$>10^4$	160
13-$_{6j}$	*p*-OEt	$>10^4$	2300	1400	24	$>10^4$	86
13-$_{6k}$	*m*-SMe	1200	1200	54	2.2	$>10^4$	2.7
13-$_{6l}$	*p*-SMe	$>10^4$	1400	110	9.1	$>10^4$	52
13-$_{6m}$	*m*-OH	2000	5100	460	51	$>10^4$	85
13-$_{6n}$	*p*-OH	$>10^4$	$>10^4$	$>10^4$	37	$>10^4$	48
13-$_{6o}$	*m*-SO_2Me	$>10^4$	$>10^4$	$>10^4$	$>10^4$	$>10^4$	N.T.
13-$_{6p}$	*p*-SO_2Me	$>10^4$	$>10^4$	$>10^4$	$>10^4$	$>10^4$	N.T.
13-$_{6q}$	*m*-CH_2OMe	$>10^4$	2100	1200	9.7	$>10^4$	3.1
13-$_{6r}$	*p*-CH_2OMe	$>10^4$	8300	1200	28	$>10^4$	62

Using membrane fractions of CHO cells expressing the prostanoid receptors, the mouse (m) EP-receptor of 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.[7] 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. N.T. = Not tested.

the potency of the agonist activity were investigated. Introduction of a methyl group provided **13-$_{6a}$**, **13-$_{6b}$** and **13-$_{6c}$** retaining good EP4-receptor selectivity, while agonist activities were increased in **13-$_{6b}$** and reduced in **13-$_{6a}$** and **13-$_{6c}$**. Introduction of a methoxy group afforded **13-$_{6f}$**, **13-$_{6g}$** and **13-$_{6h}$** retaining good EP4-receptor selectivity, while maximal reduction of the agonist activity was observed in **13-$_{6f}$**. Biological evaluation of the two series of compounds **13-$_{6a–c}$** and **13-$_{6f–h}$** clearly demonstrated that the *meta*- and *para*-isomers are much more preferred to the *ortho*-isomers. Based on this finding, *meta*- and *para*-isomers were evaluated on a variety of substituents. Introduction of a chloro group afforded **13-$_{6d}$** and **13-$_{6e}$** with increased and decreased agonist activity, respectively, although the EP3-receptor affinities of both were increased. Subtype selectivity of **13-$_{6e}$** was markedly reduced. Introduction of an ethoxy group provided **13-$_{6i}$** and **13-$_{6j}$** retaining good selectivity, while their EP4-receptor affinity and agonist activities were less potent compared with those of **1**. Of the derivatives with a methylthio group, the *meta*-isomer **13-$_{6k}$** showed more potent agonist activity retaining selectivity. Phenol derivatives **13-$_{6m}$** and **13-$_{6n}$** demonstrated increased EP4-receptor selectivity with less potent agonist activity than **1** while both the K_i and EC_{50} values were decreased. The EP4-receptor selectivity of **13-$_{6n}$** was excellent because it did not exhibit any affinity to other receptors even at 10 μM, but its agonist activity was not potent (48 nM). *meta*- and *para*-Methylsulfonylphenyl derivatives **13-$_{6o}$** and **13-$_{6p}$** did not show any affinity to any of the receptors at 10 μM. Introduction of a methoxymethyl group afforded **13-$_{6q}$** and **13-$_{6r}$** retaining good EP4-receptor affinities. The agonist activity of the *meta*-isomer **13-$_{6q}$** was excellent. Among the compounds listed in Table 1, **13-$_{6q}$** exhibited the best profile as a potent and selective EP4-receptor agonist and had a markedly weak EC_{50} value[6] (5800 nM) for its EP3-receptor affinity (K_i = 1200 nM). *para*-Phenol derivatives **13-$_{6n}$** also demonstrated excellent subtype selectivity, while both of receptor affinity and agonist activity were less potent than those of **13-$_{6q}$**.

Based on the findings described above, our further attempts at optimization were focused on introduction of the *meta*-substituent (*m*-) into the phenyl moiety of **1** as described in Table 2a and b. First, fine tuning of the *m*-methoxymethyl moiety of **13-$_{6q}$** was carried out. Although *m*-hydroxymethyl derivative **13-$_{7a}$** exhibited good EP4-receptor selectivity and the agonist activity, the K_i and EC_{50} values were less potent and almost the same as those of **1**. Replacement of the oxygen atom of the *m*-methoxymethyl moiety of **13-$_{6q}$** with a sulfur atom provided **13-$_{7b}$** with retention of the potent EP4-receptor affinity and agonist activity and increased EP3-receptor affinity. One or two carbon homologation of the methylene moiety of the *m*-substituent in **13-$_{6q}$** afforded **13-$_{7c}$** and **13-$_{7d}$** with retention of EP4-receptor selectivity while their agonist activities were nearly 4- and 15-fold less potent than that of **13-$_{6q}$**, respectively. One or two carbon homologation of the methyl group in the *m*-methoxymethyl moiety afforded **13-$_{7e}$** and **13-$_{7f}$** with retention of good EP4-receptor selectivity and potent agonist activity, respectively. The EC_{50} value of **13-$_{7e}$** was 4-fold more potent than that of **13-$_{7f}$**. Similar replacement with an allyl group afforded **13-$_{7g}$** with excellent EP4-receptor selectivity, although its EC_{50} value was nearly 4-fold less potent than that of **13-$_{6q}$**. Replacement of the propyl group in **13-$_{7f}$** with an isopropyl group afforded **13-$_{7h}$** with retention of good EP4-receptor selectivity and agonist activity. The EP4-receptor selectivity of **13-$_{7i}$** with a phenoxymethyl group was improved relative to **13-$_{6q}$**, while its EC_{50} value was nearly 10-fold less potent. Conversion of the methyl group in **13-$_{6q}$** to a cyclohexyl group provided **13-$_{7i}$** with good subtype selectivity and a markedly reduced EC_{50} value. Introduction of a methyl group into the methylene moiety in **13-$_{6q}$** afforded **13-$_{7k}$** with marked reduction of EP4-receptor affinity and the EC_{50} value.

Table 2b shows the effects of the other *meta*-substituents in the phenyl moiety of the 16-phenyl-ω-tetranor-3,7-dithiaPGE_1 on receptor affinity and the EC_{50} value. *m*-Ethyl derivative **13-$_{8a}$** exhibited moderate EP4-receptor selectivity and potent agonist activity, with a profile very close to that of the corresponding *m*-methyl derivative **13-$_{6b}$**. *m*-Vinyl derivative **13-$_{8b}$** exhibited less EP4-receptor selectivity to the receptors EP1, EP2, EP3 with a less potent EC_{50} values than **13-$_{8a}$**. *m*-Propyl derivative **13-$_{8c}$** exhibited reduced selectivity to the EP3-receptor, while its agonist activity was nearly equivalent to that of **13-$_{8a}$**. *m*-Isopropyl derivative **13-$_{8d}$** also exhibited moderate EP4-receptor selectivity, while its EC_{50} value was more than 30-fold less potent than that of **13-$_{8a}$**. Although the *m*-benzyl derivative **13-$_{8e}$** showed increased EP4-receptor selectivity, its EC_{50} value was markedly reduced. Both the receptor selectivity and the EC_{50} value were improved in *m*-(2-fluoroethyl) derivative **13-$_{8f}$**. *m*-Alkyne derivatives **13-$_{8g}$** and **13-$_{8h}$** demonstrated potent EP4-receptor affinity with moderate EC_{50} values, although their subtype selectivities were different in their affinity to the IP-receptor. *m*-Phenyl derivative **13-$_{8i}$** also exhibited IP-receptor affinity. The conjugated phenyl moiety in the *meta*-position tended to increase the IP-receptor affinity. The IP-receptor affinity was not observed in *meta*-heteroaromatic derivatives **13-$_{8j}$** and **13-$_{8k}$**, both of which exhibited moderate EP4-receptor selectivity. The EC_{50} value of **13-$_{8k}$** was 10-fold more potent than that of **13-$_{8j}$** because of its more hydrophilic properties due to the oxygen atom contained in the furyl moiety. *m*-Cyano derivative **13-$_{8l}$** showed moderate EP4-receptor selectivity in the binding assay while its EC_{50} value was markedly reduced compared with **13-$_{8a}$**. *m*-Trifluoro derivative **13-$_{8m}$** exhibited reduced selectivity because of its increased EP3-receptor affinity, while its EC_{50} value and affinity for the EP4-receptor were potent.

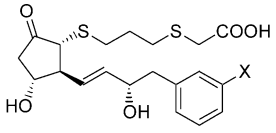
Biological evaluation of 16-(disubstituted)phenyl derivatives was conducted as shown in Table 3. Structural hybridization of **13-$_{6b}$** and **13-$_{6n}$** provided 16-(3-methyl-4-hydroxy)phenyl derivative **18-$_{14e}$**, which demonstrated excellent EP4-receptor selectivity with moderate agonist activity. 16-(3,4-Dichloro)phenyl derivative **18-$_{14a}$** showed increased EP3-receptor affinity in addition to potent EP4-receptor affinity. 3,4-Dimethoxy, 3-chloro-4-methoxy and 3-methyl-4-methoxy derivatives **18-$_{14b}$**, **18-$_{14c}$** and **18-$_{14d}$** showed the markedly reduced EC_{50}

values, while the EP4-receptor affinity was retained in **18-$_{14c}$** and **18-$_{14d}$**, and markedly reduced in **18-$_{14b}$**. Both the EP4-receptor selectivity and the EC_{50} value of 3-chloro-6-methoxy derivative **18-$_{14f}$** and 2,5-dimethyl derivative **18-$_{14g}$** were markedly reduced. 16-(2,3-Disubstituted)phenyl derivatives **18-$_{14h}$** and **18-$_{14i}$** also showed markedly reduced agonist activity with reduced EP4-receptor affinity. The EP4-receptor affinity and selectivity of 16-(3,5-disubstituted)phenyl derivatives **18-$_{14j}$** and **18-$_{14k}$** were reduced.

As shown in Table 4, replacement of the 16-phenyl moiety in **1** with miscellaneous aromatic groups was carried out to produce **18-$_{15a}$**–**18-$_{15e}$**. 16-Naphthyl derivative **18-$_{15a}$** demonstrated moderate subtype selectivity and EP4-receptor affinity, while its EC_{50} value was 2–3-fold less than that of **1**. A reduced EP4-receptor affinity was obtained in the structural conversion from **18-$_{15a}$** to **18-$_{15b}$** retaining the EC_{50} value. 16-(3-Thienyl)derivative **18-$_{15c}$** exhibited potent EP4-receptor affinity and agonist activity, while its subtype selectivity was nearly the same as that of **1**. The profile was almost retained in 16-(2-thienyl)derivative **18-$_{15d}$**. Introduction of a methoxymethyl group into position-5 of the thiophene moiety of **18-$_{15d}$** produced **18-$_{15e}$** but did not improve on the biological profile of **1**.

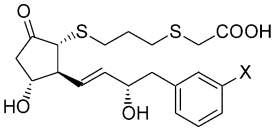
Based on the SARs mentioned above, we estimated the effects of the ω chain structure on the subtype selectivity of 3,7-dithiaPGs as described below. A lipophilic group on the *meta*-position of the 16-phenyl moiety in **1** seemed to be indispensable for the potent EP4-receptor agonist activity as illustrated in Table 1 (**13-$_{6b,6d}$**) and Table 2b (**13-$_{8a,8c,8m}$**), although most of these compounds also exhibited high affinity to the EP3-receptor. A hydrophilic group on the *meta*- or the *para*-position was found to reduce affinity to the EP3-receptor as illustrated in Table 1 (**13-$_{6g,6h,6m,6n}$**). Based on these observations, the EP3-receptor was suggested to show affinity to the lipophilic ω chain moiety. This is why introduc-

Table 2. (a) Further optimization of *m*-substituted of 16-phenyl-ω-tetranor-3,7-dithiaPGE$_1$ analogues **13-$_{7a}$**–**13-$_{7k}$**



Compound	R	Binding K_i (nM)					EC_{50} (nM)
		mEP1	mEP2	MEP3	mEP4	hlP	mEP4
13-$_{7a}$	CH_2OH	$>10^4$	8500	$>10^4$	22	$>10^4$	39
13-$_{7b}$	CH_2SMe	$>10^4$	5300	430	6.0	$>10^4$	4.8
13-$_{7c}$	CH_2CH_2OMe	$>10^4$	3100	3000	8.5	$>10^4$	12
13-$_{7d}$	$CH_2CH_2CH_2OMe$	$>10^4$	$>10^4$	$>10^4$	100	$>10^4$	44
13-$_{7e}$	CH_2OEt	$>10^4$	$>10^4$	4500	9.4	$>10^4$	2.5
13-$_{7f}$	CH_2OPr^n	$>10^4$	7700	3000	5.2	$>10^4$	10
13-$_{7g}$	$CH_2Oallyl$	$>10^4$	1300	6200	1.4	$>10^4$	12
13-$_{7h}$	CH_2OPr^i	$>10^4$	7400	1600	16	$>10^4$	6.7
13-$_{7i}$	CH_2OPh	$>10^4$	2700	1900	4.2	$>10^4$	28
13-$_{7j}$	CH_2Ohex^c	$>10^4$	$>10^4$	$>10^4$	40	$>10^4$	400
13-$_{7k}$	$CH(CH_3)OMe$	1900	$>10^4$	3800	130	$>10^4$	500

(b) Effects on the biological activities of the other *m*-substituents of the 16-phenyl-ω-tetranor-3,7-dithiaPGE$_1$analogues **13-$_{8a}$**–**13-$_{8m}$**



Compound	R	Binding K_i (nM)					EC_{50} (nM)
		mEP1	mEP2	mEP3	mEP4	hlP	mEP4
13-$_{8a}$	Et	1900	420	120	2.5	$>10^4$	2.0
13-$_{8b}$	vinyl	760	150	120	4.2	$>10^4$	12
13-$_{8c}$	Pr^n	$>10^4$	270	19	1.3	$>10^4$	4.8
13-$_{8d}$	Pr^i	$>10^4$	1600	96	7.1	$>10^4$	67
13-$_{8e}$	CH_2Ph	$>10^4$	$>10^4$	820	7.1	$>10^4$	280
13-$_{8f}$	CH_2CH_2F	2800	770	900	6.5	$>10^4$	3.7
13-$_{8g}$	—≡—Me	$>10^4$	760	200	6.3	$>10^4$	19
13-$_{8h}$	—≡—Ph	$>10^4$	550	230	0.34	150	12
13-$_{8i}$	Phenyl	$>10^4$	1100	970	1.0	770	40
13-$_{8j}$	2-thienyl	$>10^4$	680	1500	2.7	$>10^4$	42
13-$_{8k}$	2-furyl	$>10^4$	200	250	2.8	$>10^4$	3.4
13-$_{8l}$	CN	1400	5400	920	30	$>10^4$	110
13-$_{8m}$	CF_3	2000	1800	47	2.1	$>10^4$	6.1

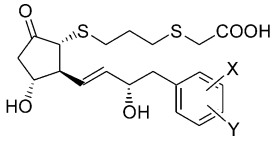
tion of a hydrophilic group into the phenyl moiety of **1** was predicted to be effective to increase the EP4-receptor selectivity.

The analysis described above yielded **18-$_{14e}$**, which was designed based on the structural hybridization of **13-$_{6b}$** and **13-$_{6n}$**. The excellent EP4-receptor selectivity of **18-$_{14e}$** was speculated to be dependent on its proper interaction with the EP4-receptor as described in Chart 1(B). However, this interaction seems unlikely in the *p*-methoxy derivative **18-$_{14d}$** due to steric repulsion as illustrated in Chart 1(C) and (D).

A similar interaction was thought to be plausible in the *m*-methoxymethyl group of **13-$_{6q}$** as described in Chart 1(A). On the basis of the biological data of **13-$_{7c}$** and **13-$_{7d}$** possessing relatively low EP3-receptor affinity, the position of the ether oxygen atom of the methoxymethyl moiety was estimated to be important to optimize their EP4-receptor agonist activity and subtype selectivity. The sizes of the lipophilic pockets of EP4-receptor were speculated to be quite limited because the EP4-receptor affinities and agonist activities of **13-$_{7k}$** and **13-$_{7j}$** were reduced. As a result, the EP4-receptor selectivity was markedly improved by introduction of a hydrophilic oxygen atom into the appropriate position of the phenyl moiety, as illustrated in **13-$_{6q}$** and **18-$_{14e}$**.

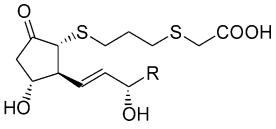
In summary, we have identified highly selective EP4-receptor agonists **13-$_{6q}$**, **13-$_{7e}$** and **18-$_{14e}$** starting from

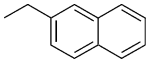
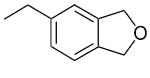
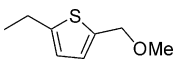
Table 3. Biological evaluation of 16-(disubstituted)phenyl-ω-tetranor 3,7-dithiaPGE$_1$



Compound	X, Y	Binding K_i (nM)					EC_{50} (nM)
		mEP1	mEP2	mEP3	mEP4	hlP	mEP4
18-$_{14a}$	3,4-dichloro	$>10^4$	4700	17	4.1	$>10^4$	45
18-$_{14b}$	3,4-dimethoxy	$>10^4$	$>10^4$	$>10^4$	250	$>10^4$	950
18-$_{14c}$	3-chloro, 4-methoxy	$>10^4$	1200	2200	11	$>10^4$	110
18-$_{14d}$	3-methyl, 4-methoxy	$>10^4$	2700	6200	20	$>10^4$	210
18-$_{14e}$	3-methyl, 4-hydroxy	$>10^4$	$>10^4$	$>10^4$	13	$>10^4$	25
18-$_{14f}$	3-chloro, 6-methoxy	$>10^4$	450	900	37	$>10^4$	290
18-$_{14g}$	2,5-dimethyl	$>10^4$	640	2000	370	$>10^4$	8400
18-$_{14h}$	2-methoxy, 3-methyl	$>10^4$	$>10^4$	$>10^4$	74	$>10^4$	630
18-$_{14i}$	2,3-dimethyl	$>10^4$	3100	870	92	$>10^4$	1600
18-$_{14j}$	3,5-dimethyl	$>10^4$	450	2000	13	$>10^4$	87
18-$_{14k}$	3-methoxy, 5-methyl	$>10^4$	1400	3300	14	$>10^4$	42

Table 4. 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
18-$_{15a}$		$>10^4$	$>10^4$	320	13	$>10^4$	100
18-$_{15b}$		$>10^4$	$>10^4$	310	65	$>10^4$	100
18-$_{15c}$		960	720	36	1.9	$>10^4$	4.4
18-$_{15d}$		570	1800	100	4.3	$>10^4$	3.7
18-$_{15e}$		$>10^4$	$>10^4$	240	13	$>10^4$	23

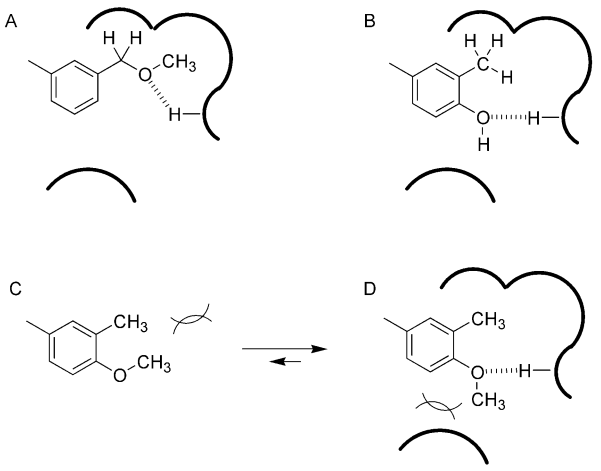


Chart 1. Interaction of the ω chain moieties with the EP4-receptor.

the detailed structural modification of **1**. The agonist activities of **13-$_{6q}$** and **13-$_{7e}$** were excellent. The EC_{50} value of **18-$_{14e}$** was nearly 10-fold less potent than the other two compounds, while its subtype selectivity was excellent. SAR of the α chain in these compounds will be discussed in the following paper.

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), acetic acid (AcOH).

(3S,4R)-1-Acetoxy-4-(*t*-butyldimethylsiloxy)-3-(*trans*-2-tributylstanylvinyl)-2-(6-methoxycarbonyl-1,5-dithiahexyl)-1-cyclopentene 4. To a stirred suspension of copper(I) cyanide (636 mg, 7.1 mmol) in freshly distilled dry THF (10 mL) was slowly added methyllithium (1.03 M in ether, 13.8 mL, 14.2 mmol) at −70 °C under Ar. The reaction mixture was warmed to 0 °C in 5 min. To the resulting clear solution was rapidly added a solution of vinyltin (4.42 g, 7.3 mmol) in THF (10 mL). After stirring for 1 h, **2** (1.84 g, 4.7 mmol) in THF (5 mL) was added dropwise to the stirred dark yellow solution at −70 °C. After stirring for 30 min, the reaction mixture was treated with acetic anhydride (1.8 mL, 18.8 mmol) and stirred at that temperature for an additional 1 h. The reaction was quenched with aq NH_4Cl/aq NH_3, (9/1) and stirred vigorously for 30 min without cooling. The orange precipitate was removed by filtration through a pad of Celite. The aqueous layer was extracted with hexane and the combined organic layer was washed with water and brine, dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (hexane–EtOAc/hexane, 1/15) to give **4** as a pale yellow oil (3.2 g, 89%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.14 (d, J = 18 Hz, 1H), 5.82 (dd, J = 18, 8 Hz, 1H), 4.25–4.15 (m, 1H), 3.72 (s, 3H), 3.21 (s, 2H), 3.25–3.15 (m, 1H), 2.9–2.3 (m, 6H), 2.18 (s, 3H), 1.9–1.7 (m, 2H), 1.6–1.2 (m, 18H), 1.0–0.8 (m, 18H), 0.06 (s, 6H).

(3S,4R)-1-Acetoxy-4-(*t*-butyldimethylsiloxy)-3-(trans-2-iodovinyl)-2-(6-methoxycarbonyl-1,5-dithiahexyl)-1-cyclopentene 5. To a stirred solution of **4** (3.2 g, 4.2 mmol) in ether (40 mL) was added iodine (1.07 g, 4.2 mmol) at room temperature. The reaction mixture was stirred for 30 min and then successively washed with saturated aqueous $Na_2S_2O_3$, aqueous KF 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 give **5** as a pale yellow oil (1.78 g, 73%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.45 (dd, J = 15, 8 Hz, 1H), 6.29 (d, J = 15 Hz, 1H), 4.2–4.1 (m, 1H), 3.72 (s, 3H), 3.22 (s, 2H), 3.25–3.15 (m, 1H), 2.85 (ddd, J = 16, 8, 2 Hz, 1H), 2.75–2.60 (m, 4H), 2.47 (ddd, J = 16, 5, 2 Hz, 1H), 2.18 (s, 3H), 1.82 (pent, J = 6 Hz, 2H), 0.87 (s,. 9H), 0.04 (s, 6H).

General procedure for the preparation of 3,7-dithia-16-Ph-PGE$_1$ derivatives

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(2-methyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6a}$. To a stirred light green suspension of chromium(II) chloride (210 mg, 1.7 mmol) and nickel(II) chloride (5 mg) in anhydrous DMF (3 mL) was added dropwise a solution of **5** (200 mg, 0.34 mmol) and an aldehyde (91 mg, 0.68 mmol) in DMF (1.5 mL) at room temperature. The resulting dark green solution was stirred for 1 h. The reaction mixture was poured into water, shaken with ether and the insoluble substances were removed by filtration through a pad of Celite. The filtrate was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/6–1/4) to give **11-$_{6a}$** as a pale yellow oil (124 mg, 60%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20–6.90 (m, 4H), 5.77 (dd, J = 16, 6 Hz, 1H), 5.75 (dd, J = 16, 8 Hz, 1H), 5.57 (m, 1H), 4.38 (m, 1H), 4.09 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.15 (m, 1H), 2.95–2.4 (m, 8H), 2.33 (s, 3H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6b}$. 67% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (m, 1H), 7.1–6.9 (m, 3H), 5.77 (dd, J = 16, 6 Hz, 1H), 5.75 (dd, J = 16, 8 Hz, 1H), 5.57 (m, 1H), 4.38 (m, 1H), 4.09 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.15 (m, 1H), 2.95–2.4 (m, 8H), 2.33 (s, 3H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(4-methyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6c}$. 74% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12 (s, 4H), 5.8–5.5 (m, 2H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.72 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.5 (m, 7H), 2.5–2.4 (m, 1H), 2.19 (s, 3H), 1.9–1.7 (m, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-chloro)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6d}$. 67% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26–7.07 (m, 4H), 5.73 (dd, J = 16, 6 Hz, 1H), 5.71 (dd, J = 16, 6 Hz, 1H), 5.56 (m, 1H), 4.37 (m, 1H), 4.07 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.14 (m, 1H), 2.9–2.4 (m, 8H), 2.2 (s, 3H), 2.0–1.8 (m, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(4-chloro)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6e}$. 72% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 5.8–5.5 (m, 2H), 4.4–4.3 (m, 1H), 4.1–4.0 (m, 1H), 3.72 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.5 (m, 7H), 2.43 (dd, J = 16, 5 Hz, 1H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(2-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6f}$. 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–6.78 (m, 4H), 5.83–5.67 (m, 1H), 5.64–5.48 (m, 1H), 4.50–4.33 (m, 1H), 4.20–4.02 (m, 1H), 3.83 (s, 3H), 3.72 (s, 2H), 3.24–3.08 (m, 3H), 3.00–2.20 (m, 9H), 2.18 (s, 3H), 1.92–1.72 (m, 2H), 0.86 (s, 9), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6g}$. Compound **11-$_{6g}$** was used for the next reaction without further purification.

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(4-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6h}$. 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 5.82–5.49 (m, 2H), 4.41–4.26 (m, 1H), 4.17–4.05 (m, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.21 (s, 2H), 3.19–3.10 (m, 1H), 2.97–2.50 (m, 7H), 2.50–2.36 (m, 1H), 2.19 (s, 3H), 1.88–1.68 (m, 2H), 0.84 (s, 9H), 0.02 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-ethoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6i}$. 91% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21–7.18 (m, 1H), 6.82–6.75 (m, 3H), 5.80–5.53 (m, 2H), 4.41–4.32 (m, 1H), 4.17–3.95 (m, 4H), 3.74 (s, 3H), 3.21 (s, 2H), 3.19–3.10 (m, 1H), 2.92–2.55 (m, 7H), 2.50–2.40 (m, 1H), 2.18 (s, 3H), 1.88–1.70 (m, 2H), 1.41 (t, J = 7.0 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(4-ethoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6j}$. 88% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.14 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.80–5.50 (m, 2H), 4.37–4.28 (m, 1H), 4.18–3.98 (m, 4H), 3.71 (s, 3H), 3.20 (s, 2H), 3.19–3.10 (m, 1H), 2.92–2.53 (m, 7H), 2.44–2.38 (m, 1H), 2.19 (s, 3H), 1.85–1.70 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methylthio)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6k}$. 66% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2–6.95 (m, 4H), 5.75 (dd, J = 16, 6 Hz, 1H), 5.73 (dd, J = 16, 6 Hz, 1H), 5.57 (dd, J = 15, 8 Hz, 1H), 4.38 (m, 1H), 4.08 (m, 1H), 3.72 (s, 3H), 3.21 (s, 2H), 3.15 (m, 1H), 2.95–2.35 (m, 8H), 2.47 (s, 3H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.86 (s, 9H), 0.02 (m, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(4-methylthio)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6l}$. 81% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.1 (m, 4H), 5.8–5.5 (m, 2H), 4.34 (m, 1H), 4.08 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.12 (m, 1H), 2.95–2.35 (m, 8H), 2.46 (s, 3H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.03 (m, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-hydroxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6m}$. 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22–7.08 (m, 1H), 6.86–6.66 (m, 2H), 5.82–5.67 (m, 1H), 5.56 (dd, J = 15.3, 8.1 Hz, 1H), 4.42–4.26 (m, 1H), 4.15–4.04 (m, 1H), 3.73 (s, 3H), 3.24–3.08 (m, 3H), 2.95–2.36 (m, 8H), 2.19 (s, 3H), 1.90–1.52 (m, 2H), 0.97 (s, 9H), 0.86 (s, 9H), 0.18 (s, 6H), 0.05 (s, 3H), 0.02 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(4-hydroxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6n}$. 77% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.80–5.43 (m, 2H), 4.38–4.23 (m, 1H), 4.15–4.04 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.19–3.10 (m, 1H), 2.95–2.36 (m, 8H), 2.19 (s, 3H), 1.88–1.64 (m, 2H), 0.97 (s, 9H), 0.87 (s, 9H), 0.18 (s, 6H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methylsulfonyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6o}$. 66% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85–7.78 (m, 2H), 7.60–7.45 (m, 2H), 5.82–5.50 (m, 2H), 4.45–4.37 (m, 1H), 4.17–4.05 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.22–3.05 (m, 1H), 3.06 (s, 3H), 2.95–2.38 (m, 8H), 2.19 (s, 3H), 1.88–1.75 (m, 2H), 1.80–1.50 (br, 1H), 0.87 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(4-methylsulfonyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6p}$. 63% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (d, 2H, J = 8 Hz), 7.45 (d, 2H, J = 8 Hz), 5.75 (dd, J = 15, 6 Hz, 1H), 5.58 (dd, J = 15, 8 Hz, 1H), 4.42 (m, 1H), 4.10 (m, 1H), 3.72 (s, 3H), 3.21 (s, 2H), 3.14 (m,

1H), 3.04 (s, 3H), 3.0–2.3 (m, 8H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.03 (m, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methoxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6q}$. 74% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 5.8–5.5 (m, 2H), 4.42 (s, 2H), 4.4–4.3 (m, 1H), 4.15–4.05 (m, 1H), 3.74 (s, 3H), 3.40 (m, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.4 (m, 8H), 2.18 (s, 3H), 1.9–1.7 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(4-methoxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{6r}$. 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.2 (m, 4H), 5.8–5.5 (m, 2H), 4.42 (s, 2H), 4.5–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.73 (s, 3H), 3.38 (m, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.4 (m, 8H), 2.21 (s, 3H), 1.9–1.7 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-hydroxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7a}$. 79% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.05 (m, 4H), 5.76 (dd, J = 15, 5.8 Hz, 1H), 5.58 (m, 1H), 4.72 (s, 2H), 4.38 (m, 1H), 4.09 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.15 (m, 1H), 2.97–2.37 (m, 8H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.94 (s, 9H), 0.87 (s, 9H), 0.06 (1m, 2H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methylthiomethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7b}$. 90% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–6.94 (m, 4H), 5.80–5.46 (m, 2H), 4.44–4.30 (m, 1H), 4.20–4.02 (m, 1H), 3.73 (s, 3H), 3.65 (s, 2H), 3.24–3.10 (m, 3H), 2.98–2.34 (m, 10H), 2.19 (s, 3H), 2.00 (s, 3H), 1.90–1.60 (m, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methoxyethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7c}$. 75% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.05 (m, 4H), 5.84–5.50 (m, 2H), 4.41–4.30 (m, 1H), 4.17–4.04 (m, 1H), 3.73 (s, 3H), 3.60 (t, J = 7.0 Hz, 2H), 3.36 (s, 3H), 3.21 (s, 2H), 3.20–3.10 (m, 1H), 2.95–2.37 (m, 10H), 2.19 (s, 3H), 1.90–1.75 (m, 2H), 1.70–1.50 (br, 1H), 0.87 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methoxypropyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7d}$. 85% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–6.92 (m, 4H), 5.84–5.68 (m, 1H), 5.57 (dd, J = 15.3, 8.5 Hz, 1H), 4.44–4.28 (m, 1H), 4.15–4.05 (m, 1H), 3.72 (s, 3H), 3.45–3.25 (m, 5H), 3.25–3.10 (m, 3H), 2.96–2.35 (m, 10H), 2.18 (s, 3H), 2.00–1.73 (m, 4H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-ethoxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7e}$. 84% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46–7.02 (m, 4H), 5.84–5.68 (m, 1H), 5.66–5.49 (m, 1H), 4.58–4.32 (m, 3H), 4.18–4.04 (m, 1H), 3.72 (s, 3H), 3.67–3.45 (m, 2H), 3.26–3.10 (m, 3H), 2.95–2.37 (m, 8H), 2.19 (s, 3H), 1.96–1.70 (m, 3H), 1.32–1.17 (m, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-propoxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7f}$. 78% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.11 (m, 4H), 5.84–5.51 (m, 2H), 4.49 (s, 2H), 4.38 (m, 1H), 4.10 (m, 1H), 3.73 (s, 3H), 3.44 (t, J = 7 Hz, 2H), 3.21 (s, 2H), 3.16 (m, 1H), 2.95–2.37 (m, 8H), 2.19 (s, 3H), 1.81–1.53 (m, 4H), 0.95 (t, J = 7 Hz, 3H), 0.87 (s, 9H), 0.04 (m, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-allyloxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7g}$. 77% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43–7.10 (m, 4H), 6.08–5.85 (m, 1H), 5.84–5.68 (m, 1H), 5.57 (dd, J = 15.4, 8.4 Hz, 1H), 5.39–5.15 (m, 2H), 4.50 (s, 2H), 4.46–4.30 (m, 1H), 4.19–3.97 (m, 3H), 3.72 (s, 3H), 3.20 (s, 2H), 3.19–3.09 (m, 1H), 2.95–2.37 (m, 8H), 2.19 (s, 3H), 1.92–1.68 (m, 2H), 0.86 (s, 9H), 0.03 (m, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-isopropoxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7h}$. 65% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 5.8–5.5 (m, 2H), 4.42 (s, 2H), 4.4–4.3 (m, 1H), 4.15–4.05 (m, 1H), 3.74 (s, 3H), 3.40 (m, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.4 (m, 8H), 2.18 (s, 3H), 1.9–1.7 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-phenoxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7i}$. 87% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.14 (m, 6H), 7.03–6.90 (m, 3H), 5.77 (dd, J = 15, 5.8 Hz, 1H), 5.58 (dd, J = 15, 8.3 Hz, 1H), 5.05 (s, 2H), 4.40 (m, 1H), 4.11 (m, 1H), 3.72 (s, 3H), 3.20 (s, 2H), 3.17 (m, 1H), 2.98–2.37 (m, 8H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-cyclohexyloxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7j}$. 51% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.09 (m, 4H), 5.85–5.69 (m, 1H), 5.57 (dd, J = 15.8, 8.2 Hz, 1H), 4.52 (s, 2H), 4.45–4.30 (m, 1H), 4.19–4.04 (m, 1H), 3.72 (s, 3H), 3.44–3.26 (m, 1H), 3.20 (s, 2H), 3.19–3.10 (m, 1H), 2.96–2.36 (m, 8H), 2.18 (s, 3H), 2.06–1.14 (m, 13H), 0.86 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-[3-(1-methoxyethyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{7k}$. 64% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.2 (m, 4H), 5.8–5.5 (m, 2H), 4.42 (s, 2H), 4.5–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.73 (s, 3H), 3.38 (m, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.4 (m, 8H), 2.21 (s, 3H), 1.9–1.7 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-ethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8a}$. 93% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.00 (m, 4H), 5.84–5.69 (m, 1H), 5.58 (dd, J = 15.4, 8.5 Hz, 1H), 4.45–4.28 (m, 1H), 4.16–4.04 (m, 1H), 3.72 (s, 3H), 3.23–3.08 (m, 3H), 3.00–2.36 (m, 10H), 2.18 (s, 3H), 1.92–1.70 (m, 4H), 1.70–1.52 (br, 1H), 1.22 (t, J = 7.7 Hz, 3H), 0.86 (s, 3H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-vinyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8b}$. 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46–7.04 (m, 4H), 6.69 (dd, J = 17.8, 10.6 Hz, 1H), 5.86–5.66 (m, 2H), 5.56 (dd, J = 15.4, 8.0 Hz, 1H), 5.23 (d, J = 10.6 Hz, 1H), 4.47–4.30 (m, 1H), 4.20–4.00 (m, 1H), 3.72 (s, 3H), 3.26–3.08 (m, 3H), 2.97–2.38 (m, 8H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.86 (s, 9H), 0.02 (m, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-propyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8c}$. 77% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.25 (m, 1H), 7.07 (d, J = 2 Hz, 1H), 7.00 (d, J = 5 Hz, 1H), 5.8–5.5 (m, 2H), 4.45–4.3 (m, 1H), 4.15–4.05 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.6 (m, 7H), 2.42 (dd, J = 16, 4 Hz, 1H), 2.20 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-isopropyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8d}$. 63% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12 (s, 4H), 5.8–5.5 (m, 2H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.72 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.5 (m, 7H), 2.5–2.4 (m, 1H), 2.19 (s, 3H), 1.9–1.7 (m, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-benzyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8e}$. 66% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37–7.00 (m, 9H), 5.75 (dd, J = 16, 6.0 Hz, 1H), 5.57 (dd, J = 16, 8.5 Hz, 1H), 4.37 (m, 1H), 4.10 (m, 1H), 3.96 (s, 2H), 3.72 (s, 3H), 3.20 (s, 2H), 3.16 (m, 1H), 2.97–2.38 (m, 8H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.03 (m, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-[3-(2-fluoroethyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8f}$. 84% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.04 (m, 4H), 5.81–5.50 (m, 2H), 4.80–4.30 (m, 3H), 4.18–4.05 (m, 1H), 3.68 (s, 3H), 3.21 (s, 2H), 3.21–2.37 (m, 10H), 2.20 (s, 3H), 1.90–1.70 (m, 2H), 1.90–1.60 (br, 1H), 0.88 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-[3-(1-propynyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8g}$. 69% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 5.8–5.5 (m, 2H), 4.42 (s, 2H), 4.4–4.3 (m, 1H), 4.15–4.05 (m, 1H), 3.74 (s, 3H), 3.40 (m, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.4 (m, 8H), 2.18 (s, 3H), 1.9–1.7 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-[3-(2-phenylethynyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate11-$_{8h}$. 60% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.16 (m, 9H), 5.83–5.48 (m, 2H), 4.48–4.32 (m, 1H), 4.20–4.00 (m, 1H), 3.72 (s, 3H), 3.24–3.08 (m, 3H), 2.96–2.32 (m, 8H), 2.18 (s, 3H), 1.90–1.50 (m, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-phenyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8i}$. 75% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66–7.16 (m, 9H), 5.88–5.69 (m, 1H), 5.58 (dd, J = 15.8, 8.2 Hz, 1H), 4.52–4.36 (m, 1H), 4.16–4.02 (m, 1H), 3.71 (s, 3H), 3.24–3.08 (m, 3H), 2.96–2.32 (m, 8H), 2.18 (s, 3H), 1.90–1.50 (m, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-[3-(2-thienyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8j}$. 90% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55–7.00 (m, 7H), 5.85–5.70 (m, 1H), 5.58 (dd, J = 15.4, 8.4 Hz, 1H), 4.51–4.34 (m, 1H), 4.16–4.00 (m, 1H), 3.72 (s, 3H), 3.24–3.08 (m, 1H), 3.00–2.34 (m, 8H), 2.19 (s, 3H), 1.90–1.54 (m, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-[3-(2-furyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8k}$. 86% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55–7.45 (m, 2H), 7.46 (d, J = 1.5 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.13 (m, 1H), 6.65 (d, J = 3.4 Hz, 1H), 6.46 (dd, J = 3.4, 1.5 Hz, 1H), 5.77 (dd, J = 15, 5.7 Hz, 1H), 5.58 (dd, J = 15, 8.5 Hz, 1H), 4.42 (m, 1H), 4.08 (m, 1H), 3.72 (s, 3H), 3.20 (s, 2H), 3.13 (m, 1H), 2.98–2.34 (m, 8H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-cyano)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8l}$. 60% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 5.8–5.5 (m, 2H), 4.42 (s, 2H), 4.4–4.3 (m, 1H), 4.15–4.05 (m, 1H), 3.74 (s, 3H), 3.40 (m, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.4 (m, 8H), 2.18 (s, 3H), 1.9–1.7 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-trifluoromethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 11-$_{8m}$. 72% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63–7.28 (m, 4H), 5.82–5.66 (m, 1H), 5.57 (dd, J = 15.5, 7.5 Hz, 1H), 4.49–4.32 (m, 1H), 4.14–4.00 (m, 1H), 3.72 (s, 3H), 3.24–3.07 (m, 3H), 2.95–2.34 (m, 8H), 2.18 (s, 3H), 1.97–1.70 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3,4-dichloro)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14a}$. 73% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.30 (m, 2H), 7.13–7.04 (m, 1H), 5.80–5.64 (m, 1H), 5.55 (dd, J = 15.4, 7.6 Hz, 1H), 4.45–4.27 (m, 1H), 4.13–4.02 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.19–3.08 (m, 1H), 2.98–2.32 (m, 10H), 2.19 (s, 3H), 1.92–1.70 (m, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3,4-dimethoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14b}$. 90% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.98–6.60 (m, 3H), 5.82–5.53 (m, 2H), 4.40–4.27 (m, 1H), 4.15–4.05 (m, 1H), 3.92–3.80 (m, 6H), 3.73 (s, 3H), 3.23–3.10 (m, 3H), 2.90–2.36 (m, 8H), 2.18 (s, 3H), 1.90–1.64 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-chloro-4-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14c}$. Compound **16-$_{14c}$** was used for the next reaction without further purification.

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methyl-4-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14d}$. 89% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05–6.95 (m, 2H), 6.76 (d, J = 8.6 Hz, 1H), 5.76 (dd, J = 16, 6.1 Hz, 1H) 5.74 (dd, J = 16, 5.5 Hz, 1H), 5.57 (dd, J = 16, 8.3 Hz, 1H), 4.31 (m, 1H), 4.11 (m, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.21 (s, 2H), 3.16 (m, 1H), 2.97–2.36 (m, 8H), 2.19 (s, 6H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methyl-4-hydroxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14e}$. 66% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.99 (m, 1H), 6.90 (dd, J = 8.2, 2.2 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 5.74 (dd, J = 15, 5.8 Hz, 1H), 5.56 (m, 1H), 4.31 (m, 1H), 4.10 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.13 (m, 1H), 2.97–2.35 (m, 8H), 2.19 (s, 3H), 2.18 (s, 3H), 1.9–1.7 (m, 2H), 1.01 (s, 9H), 0.87 (s, 9H), 0.20 (s, 6H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-chloro-6-methoxyphenyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14f}$. Compound **16-$_{14f}$** was used for the next reaction without further purification.

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(2,5-dimethylphenyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14g}$. 86% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12–6.91 (m, 3H), 5.84–5.73 (m, 1H), 5.58 (dd, J = 15.4, 8.7 Hz, 1H), 4.41–4.32 (m, 1H), 4.18–4.04 (m, 1H), 3.72 (s, 3H), 3.24–3.11 (m, 1H), 3.00–2.32 (m, 8H), 2.29 (s, 6H), 2.18 (s, 3H), 1.90–1.72 (m, 2H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(2-methoxy-3-methylphenyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14h}$. 65% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.1–6.9 (m, 3H), 5.8–5.7 (m, 1H), 5.65–5.5 (m, 1H), 4.45–4.35 (m, 1H), 4.1–4.05 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 2.9–2.4 (m, 8H), 2.30 (s, 3H), 2.20 (s, 3H), 1.9–1.7 (m, 2H), 0.90 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(2,3-dimethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14i}$. 68% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12 (s, 4H), 5.8–5.5 (m, 2H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.72 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.5 (m, 7H), 2.5–2.4 (m, 1H), 2.19 (s, 3H), 1.9–1.7 (m, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3,5-dimethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14j}$. 91% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.89–6.82 (m, 3H), 5.83–5.68 (m, 1H), 5.58 (dd, J = 15.4, 8.2 Hz, 1H), 4.43–4.28 (m, 1H), 4.18–4.04 (m, 1H), 3.72 (s, 3H), 3.24–3.08 (m, 1H), 2.96–2.32 (m, 8H), 2.29 (s, 6H), 2.18 (s, 3H), 1.90–1.72 (m, 2H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-methoxy-5-methyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{14k}$. 61% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12 (s, 4H), 5.8–5.5 (m, 2H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.72 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.5 (m, 7H), 2.5–2.4 (m, 1H), 2.19 (s, 3H), 1.9–1.7 (m, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(2-naphtyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{15a}$. 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98–7.28 (m, 7H), 5.87–5.70 (m, 1H), 5.56 (dd, 1H, J = 15, 8.8 Hz), 4.56–4.40 (m, 1H), 4.12–3.98 (m, 1H), 3.71 (s, 3H), 3.24–3.06 (m, 3H), 3.06–2.30 (m, 8H), 2.18 (s, 3H), 1.90–1.68 (m, 2H), 1.68–1.50 (br, 1H), 0.85 (s, 9H), 0.00 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(5-isocoumaranyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{15b}$. 72% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2–7.0 (m, 3H), 5.76 (dd, J = 15, 5.6 Hz, 1H), 5.57 (dd, 1H, J = 15, 8.1 Hz), 5.08 (s, 4H), 4.38 (m, 1H), 4.10 (m, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 3.15 (m, 1H), 2.98–2.38 (m, 8H), 2.19 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(3-thienyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{15c}$. 71% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.25 (m, 1H), 7.07 (d, J = 2 Hz, 1H), 7.00 (d, J = 5 Hz, 1H), 5.8–5.5 (m, 2H), 4.45–4.3 (m, 1H), 4.15–4.05 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.6 (m, 7H), 2.42 (dd, J = 16, 4 Hz, 1H), 2.20 (s, 3H), 1.9–1.7 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-(2-thienyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{15d}$. 62% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16 (dd, J = 5.1, 1.3 Hz, 1H), 7.93 (dd, J = 5.1, 3.3 Hz, 1H), 6.91–6.84 (m, 1H), 5.82–5.51 (m, 2H), 4.46–4.28 (m, 1H), 4.20–4.04 (m, 1H), 3.72 (s, 3H), 3.24–3.10 (m, 3H), 3.10–2.35 (m, 9H), 2.18 (s, 3H), 1.90–1.72 (m, 2H), 0.86 (s, 9H), 0.04–0.02 (m, 6H).

Methyl 9-acetoxy-11,15-bis(*t*-butyldimethylsiloxy)-16-[3-(5-methoxymethyl)thienyl]-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 16-$_{15e}$. 56% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12 (s, 4H), 5.8–5.5 (m, 2H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.72 (s, 3H), 3.22 (s, 2H), 3.2–3.1 (m, 1H), 3.0–2.5 (m, 7H), 2.5–2.4 (m, 1H), 2.19 (s, 3H), 1.9–1.7 (m, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(2-methyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6a}$. To a stirred solution of **11-$_{6a}$** (124 mg, 0.20 mmol) and pyridine (0.1 mL) in acetonitrile (3 mL) was added pyridinium poly(hydrogen fluoride) [$(HF)_n$•py, Aldrich, 0.2 mL]. The reaction mixture was stirred for 30 min without cooling and then slowly poured into a heterogeneous mixture of EtOAc and saturated aqueous $NaHCO_3$ with stirring. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with 1 N HCl, H_2O and brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the residual two diastereomers were separated by column chromatography on silica gel (EtOAc/hexane, 1/1–3/1

then EtOAc/AcOH, 100/1) to give a more polar product **12-$_{6a}$** as a yellow oil (32 mg, 31%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20–7.07 (m, 4H), 5.76 (dd, J = 15.4, 6.4 Hz, 1H), 5.56 (dd, J = 15.4, 8.2 Hz, 1H), 4.43–4.27 (m, 1H), 4.15–4.01 (m, 1H), 3.72 (s, 3H), 3.27–3.16 (m, 3H), 3.08–2.40 (m, 8H), 2.33 (s, 3H), 2.19 (s, 3H), 1.92–1.71 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6b}$. 41% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19 (m, 1H), 7.03 (m, 3H), 5.76 (dd, J = 15, 6 Hz), 5.58 (dd, J = 15, 8 Hz), 4.37 (m, 1H), 4.08 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.21 (m, 1H), 3.0–2.4 (m, 8H), 2.33 (s, 3H), 2.20 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(4-methyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6c}$. 41% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.09 (s, 4H), 5.74 (dd, J = 15, 6 Hz, 1H), 5.56 (dd, J = 15, 8 Hz, 1H), 4.35–4.3 (m, 1H), 4.1–4.05 (m, 1H), 3.70 (s, 3H), 3.22 (s, 2H), 3.25–3.2 (m, 1H), 2.92 (dd, J = 17, 7 Hz, 1H), 2.83 (dd, J = 14, 5 Hz, 1H), 2.8–2.6 (m, 4H), 2.57 (dt, J = 14, 8 Hz, 1H), 2.45 (dd, J = 17, 3 Hz, 1H), 2.30 (s, 3H), 2.16 (s, 3H), 1.9–1.8 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-chloro)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6d}$. 46% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.1 (m, 4H), 5.73 (dd, J = 16, 6 Hz, 1H), 5.55 (dd, J = 16, 8 Hz), 4.37 (m, 1H), 4.07 (m, 1H), 3.74 (s, 3H), 3.23 (s, 2H), 3.21 (m, 1H), 3.0–2.4 (m, 8H), 2.20 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(4-chloro)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6e}$. 47% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (d, J = 8 Hz, 2H), 7.16 (d, J = 8 Hz, 2H), 5.74 (dd, J = 16, 6 Hz, 1H), 5.55 (dd, J = 16, 8 Hz, 1H), 4.4–4.3 (m, 1H), 4.1–4.0 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.3–3.2 (m, 1H), 2.94 (dd, J = 16, 6 Hz, 1H), 2.9–2.4 (m, 7H), 2.20 (s, 3H), 1.9–1.8 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(2-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6f}$. 45% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28–7.08 (m, 2H), 6.96–6.80 (m, 2H), 5.71 (dd, J = 15.4, 6.4 Hz, 1H), 5.52 (dd, J = 15.4, 8.2 Hz, 1H), 4.47–4.32 (m, 1H), 4.11–3.99 (m, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.24–3.10 (m, 3H), 2.98–2.36 (m, 8H), 2.18 (s, 3H), 1.88–1.68 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6g}$. 39% yield in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.15 (m, 1H), 6.8–6.7 (m, 3H), 5.77 (dd, J = 15, 6 Hz, 1H), 5.57 (dd, J = 15, 8 Hz, 1H), 4.4–4.3 (m, 1H), 4.15–4.0 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.22 (s, 2H), 3.3–3.2 (m, 1H), 3.0–2.4 (m, 9H), 2.20 (s, 3H), 1.9–1.7 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(4-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6h}$. 45% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.13 (d, J = 8 Hz, 2H), 6.85 (d, J = 8 Hz, 2H), 5.76 (dd, J = 16, 6 Hz, 1H), 5.56 (dd, J = 16, 8 Hz, 1H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.22 (s, 2H), 3.3–3.2 (m, 1H), 2.94 (dd, J = 16, 6 Hz, 1H), 2.8–2.4 (m, 7H), 2.22 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-ethoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6i}$. 43% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28–7.15 (m, 1H), 6.80–6.70 (m, 3H), 5.75 (dd, J = 15.4, 6.2 Hz, 1H), 5.55 (dd, J = 15.4, 8.0 Hz, 1H), 4.41–4.31 (m, 1H), 4.10–4.05 (m, 1H), 4.02 (q, J = 7.0 Hz, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.22–3.18 (m, 1H), 3.00–2.00 (br, 2H), 2.97–2.42 (m, 8H), 2.20 (s, 3H), 1.88–1.72 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(4-ethoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6j}$. 40% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.74 (dd, J = 15.4, 6.2 Hz, 1H), 5.55 (dd, J = 15.4, 8.4 Hz, 1H), 4.36–4.27 (m, 1H), 4.10–4.04 (m, 1H), 4.01 (q, J = 7.0 Hz, 2H), 3.73 (s, 3H), 3.22 (s, 2H), 3.22–3.15 (m, 1H), 2.91 (ddd, J = 16.6, 6.8, 1.2 Hz, 1H), 2.80–2.40 (m, 7H), 2.50–2.20 (br, 2H), 2.20 (s, 3H), 1.87–1.73 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methylthio)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6k}$. 42% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22 (m, 1H), 7.15–7.05 (m, 2H), 6.99 (m, 1H), 5.73 (dd, J = 15, 6 Hz, 1H), 5.55 (dd, J = 15, 8 Hz, 1H), 4.36 (m, 1H), 4.07 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.21 (m, 1H), 2.95–2.4 (m, 8H), 2.47 (s, 3H), 2.20 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(4-methylthio)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6l}$. 43% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.1 (m, 4H), 5.73 (1H, J = 16, 6 Hz, 1H), 5.55 (dd, J = 16, 8 Hz, 1H), 4.34 (m, 1H), 4.08 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.20 (m, 1H), 3.0–2.4 (m, 8H), 2.47 (s, 3H), 2.20 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-hydroxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6m}$. 35% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22–7.06 (m, 1H), 6.94–6.56 (m, 4H), 5.72 (dd, J = 15.4, 6.6 Hz, 1H), 5.52 (dd, J = 15.4, 8.0 Hz, 1H), 4.45–4.25 (m, 1H), 4.14–3.98 (m, 1H), 3.73 (s, 3H), 3.30–3.12 (m, 3H), 3.02–2.36 (m, 10H), 2.20 (s, 3H), 1.92–1.70 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(4-hydroxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6n}$. 38% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.04 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 6.60–6.40 (br, 1H), 5.69 (dd, J = 15.4, 6.2 Hz, 1H), 5.50 (dd, J = 15.4, 8.0 Hz, 1H), 4.35–4.25 (m, 1H), 4.13–4.00 (m, 1H), 3.74 (s, 3H), 3.60–3.20 (br, 1H), 3.22 (s, 2H), 3.22–3.12 (m, 1H), 2.94–2.42 (m, 8H), 2.20 (s, 3H), 2.20–2.00 (br, 1H), 1.82–1.70 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methylsulfonyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6o}$. 39% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H), 7.54–7.45 (m, 2H), 5.75 (dd, J = 15.4, 5.8 Hz,

1H), 5.54 (dd, $J=15.4$, 8.0 Hz, 1H), 4.48–4.39 (m, 1H), 4.10–4.02 (m, 1H), 3.73 (s, 3H), 3.23 (s, 2H), 3.23–3.17 (m, 1H), 3.06 (s, 3H), 2.96–2.20 (m, 10H), 2.19 (s, 3H), 1.87–1.73 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(4-methylsulfonyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6p}$. 40% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85 (d, $J=8$ Hz, 2H), 7.44 (d, $J=8$ Hz, 2H), 5.72 (dd, $J=16$, 6 Hz, 1H), 5.54 (dd, $J=16$, 8 Hz, 1H), 4.40 (m, 1H), 4.05 (m, 1H), 3.73 (s, 3H), 3.23 (s, 2H), 3.21 (m, 1H), 3.04 (s, 3H), 2.99–2.52 (m, 7H), 2.45 (dd, $J=17$, 3 Hz, 1H), 2.20 (s, 3H), 1.82 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methoxymethyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6q}$. 48% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (t, $J=8$ Hz, 1H), 7.2–7.1 (m, 3H), 5.77 (dd, $J=15$, 7 Hz, 1H), 5.54 (dd, $J=15$, 9 Hz, 1H), 4.42 (d, $J=6$ Hz, 2H), 4.45–4.4 (m, 1H), 4.1–4.0 (m, 1H), 3.74 (s, 3H), 3.42 (m, 3H), 3.22 (s, 2H), 3.25–3.2 (m, 1H), 3.0–2.6 (m, 8H), 2.48 (dd, $J=18$, 5 Hz, 1H), 2.19 (s, 3H), 1.9–1.8 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(4-methoxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{6r}$. 49% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (d, $J=8$ Hz, 2H), 7.21 (d, $J=8$ Hz, 2H), 5.77 (dd, $J=15$, 6 Hz, 1H), 5.56 (dd, $J=15$, 8 Hz, 1H), 4.42 (s, 2H), 4.45–4.3 (m, 1H), 4.15–4.0 (m, 1H), 3.73 (s, 3H), 3.38 (m, 3H), 3.3–3.2 (m, 1H), 3.23 (s, 2H), 3.0–2.3 (m, 9H), 2.20 (s, 3H), 1.9–1.8 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-hydroxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7a}$. 41% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31–7.07 (m, 4H), 5.68 (dd, $J=15$, 6.4 Hz, 1H), 5.49 (dd, $J=15$, 8.6 Hz, 1H), 4.61 (s, 2H), 4.34 (m, 1H), 4.00 (m, 1H), 3.72 (s, 3H), 3.21 (s, 2H), 3.17 (m, 1H), 2.90–2.38 (m, 10H), 2.19 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methylthiomethyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7b}$. 43% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.05 (m, 4H), 5.73 (dd, $J=15.6$, 6.2 Hz, 1H), 5.55 (dd, $J=15.4$, 8.0 Hz, 1H), 4.44–4.30 (m, 1H), 4.14–4.02 (m, 1H), 3.73 (s, 3H), 3.65 (s, 2H), 3.26–3.14 (m, 3H), 2.95–2.26 (m, 10H), 2.19 (s, 3H), 2.00 (s, 3H), 1.90–1.75 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methoxyethyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7c}$. 42% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27–7.02 (m, 4H), 5.74 (dd, $J=15.6$, 6.2 Hz, 1H), 5.56 (dd, $J=15.6$, 8.2 Hz, 1H), 4.40–4.31 (m, 1H), 4.10–4.03 (m, 1H), 3.73 (s, 3H), 3.60 (t, $J=7.0$ Hz, 2H), 3.35 (s, 3H), 3.22 (s, 2H), 3.22–3.16 (m, 1H), 3.00–2.40 (m, 9H), 2.20 (s, 3H), 2.10–2.00 (br, 1H), 1.89–1.73 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methoxypropyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7d}$. 46% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–6.97 (m, 4H), 5.74 (dd, $J=15.4$, 6.4 Hz, 1H), 5.55 (dd, $J=15.4$, 8.0 Hz, 1H), 4.44–4.28 (m, 1H), 4.14–4.01 (m, 1H), 3.72 (s, 3H), 3.38 (t, $J=6.4$ Hz, 2H), 3.34 (s, 3H), 3.31–3.14 (m, 3H), 3.02–3.23 (m, 12H), 2.19 (s, 3H), 1.97–1.72 (m, 4H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-ethoxymethyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7e}$. 45% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.09 (m, 4H), 5.75 (dd, $J=15.4$, 6.0 Hz, 1H), 5.53 (dd, $J=15.4$, 8.4 Hz, 1H), 4.47 (s, 2H), 4.45–4.32 (m, 1H), 4.10–3.98 (m, 1H), 3.73 (s, 3H), 3.57 (q, $J=7.0$ Hz, 2H), 3.27–3.14 (m, 3H), 2.95–2.24 (m, 10H), 2.19 (s, 3H), 1.96–1.70 (m, 3H), 1.25 (t, $J=7.0$ Hz, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-propoxymethyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7f}$. 36% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.10 (m, 4H), 5.96 (ddt, $J=17.2$, 10.2, 6.0 Hz, 1H), 5.74 (dd, $J=15.4$, 5.8 Hz, 1H), 5.53 (dd, $J=15.4$, 8.2 Hz, 1H), 5.38–5.17 (m, 2H), 4.49 (s, 2H), 4.42–4.31 (m, 1H), 4.12–4.00 (m, 3H), 3.73 (s, 3H), 3.25–3.14 (m, 1H), 2.96–2.40 (m, 10H), 2.19 (s, 3H), 1.90–1.72 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-allyloxymethyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7g}$. 41% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43–7.10 (m, 4H), 6.08–5.85 (m, 1H), 5.84–5.68 (m, 1H), 5.57 (dd, $J=15.4$, 8.4 Hz, 1H), 5.39–5.15 (m, 2H), 4.50 (s, 2H), 4.46–4.30 (m, 1H), 4.19–3.97 (m, 3H), 3.72 (s, 3H), 3.20 (s, 2H), 3.19–3.09 (m, 1H), 2.95–2.37 (m, 8H), 2.19 (s, 3H), 1.92–1.68 (m, 2H), 0.86 (s, 9H), 0.03 (m, 6H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-isopropoxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7h}$. 43% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (t, $J=8$ Hz, 1H), 7.2–7.1 (m, 3H), 5.77 (dd, $J=15$, 7 Hz, 1H), 5.54 (dd, $J=15$, 9 Hz, 1H), 4.42 (d, $J=6$ Hz, 2H), 4.45–4.4 (m, 1H), 4.1–4.0 (m, 1H), 3.74 (s, 3H), 3.42 (m, 3H), 3.22 (s, 2H), 3.25–3.2 (m, 1H), 3.0–2.6 (m, 8H), 2.48 (dd, $J=18$, 5 Hz, 1H), 2.19 (s, 3H), 1.9–1.8 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-phenoxymethyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7i}$. 40% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36–7.12 (m, 6H), 6.96 (m, 3H), 5.72 (dd, $J=15$, 6.3 Hz, 1H), 5.54 (dd, $J=15$, 8.3 Hz, 1H), 5.02 (s, 2H), 4.36 (m, 1H), 4.05 (m, 1H), 3.72 (s, 3H), 3.20 (s, 2H), 3.19 (m, 1H), 2.95–2.39 (m, 10H), 2.18 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-cyclohexyloxymethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7j}$. 46% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.08 (m, 4H), 5.74 (dd, $J=15.4$, 6.2 Hz, 1H), 5.57 (dd, $J=15.4$, 8.4 Hz, 1H), 4.51 (s, 2H), 4.45–4.32 (m, 1H), 4.09–3.96 (m, 1H), 3.73 (s, 3H), 3.45–3.28 (m, 1H), 3.26–3.02 (m, 3H), 2.96–2.40 (m, 10H), 2.19 (s, 3H), 2.06–1.15 (m, 12H).

Methyl 9-acetoxy-11,15-dihydroxy-16-[3-(1-methoxyethyl)]-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{7k}$. 37% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (d, $J=8$ Hz, 2H), 7.21 (d, $J=8$ Hz, 2 H), 5.77 (dd, $J=15$, 6 Hz, 1H), 5.56 (dd, $J=15$, 8 Hz, 1H), 4.42 (s, 2H), 4.45–

4.3 (m, 1H), 4.15–4.0 (m, 1H), 3.73 (s, 3H), 3.38 (m, 3H), 3.3–3.2 (m, 1H), 3.23 (s, 2H), 3.0–2.3 (m, 9H), 2.20 (s, 3H), 1.9–1.8 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-ethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8a}$. 43% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–6.97 (m, 4H), 5.76 (dd, J = 15.4, 5.8 Hz, 1H), 5.58 (dd, J = 15.4, 8.0 Hz, 1H), 4.44–4.30 (m, 1H), 4.14–4.04 (m, 1H), 3.73 (s, 3H), 3.18–3.16 (m, 3H), 3.00–2.40 (m, 10H), 2.20 (s, 3H), 2.12–1.7 (m, 4H), 1.22 (t, J = 7.7 Hz, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-vinyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8b}$. 40% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46–7.04 (m, 4H), 6.69 (dd, J = 17.8, 10.6 Hz, 1H), 5.86–5.66 (m, 2H), 5.56 (dd, J = 15.4, 8.0 Hz, 1H), 5.23 (d, J = 10.6 Hz, 1H), 4.47–4.30 (m, 1H), 4.20–4.00 (m, 1H), 3.72 (s, 3H), 3.26–3.08 (m, 3H), 2.97–2.38 (m, 8H), 2.19 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-propyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8c}$. 44% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.2 (m, 1H), 7.06 (d, J = 2 Hz, 1H), 6.99 (dd, J = 5, 2 Hz, 1H), 5.76 (dd, J = 15, 6 Hz, 1H), 5.58 (dd, J = 15, 8 Hz, 1H), 4.45–4.3 (m, 1H), 4.15–4.05 (m, 1H), 3.73 (s, 3H), 3.3–3.2 (m, 1H), 3.22 (s, 2H), 3.0–2.4 (m, 9H), 2.20 (s, 3H), 1.9–1.7 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-isopropyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8d}$. 47% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.13 (d, J = 8 Hz, 2H), 6.85 (d, J = 8 Hz, 2H), 5.76 (dd, J = 16, 6 Hz, 1H), 5.56 (dd, J = 16, 8 Hz, 1H), 4.4–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.22 (s, 2H), 3.3–3.2 (m, 1H), 2.94 (dd, J = 16, 6 Hz, 1H), 2.8–2.4 (m, 7H), 2.22 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-benzyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8e}$. 43% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.12 (m, 6H), 7.1–6.95 (m, 3H), 5.71 (dd, J = 16, 6.2 Hz, 1H), 5.55 (dd, J = 16, 8.3 Hz, 1H), 4.32 (m, 1H), 4.04 (m, 1H), 3.95 (s, 2H), 3.72 (s, 3H), 3.21 (s, 2H), 3.19 (m, 1H), 2.95–2.38 (m, 10H), 2.19 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-[3-(2-fluoroethyl)]-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8f}$. 40% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29–7.07 (m, 4H), 5.74 (dd, J = 15.4, 6.2 Hz, 1H), 5.56 (dd, J = 15.4, 8.4 Hz, 1H), 4.63 (q, J = 6.8 Hz, 2H,), 4.41–4.31 (m, 1H), 4.09–4.00 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.22–3.17 (m, 1H), 3.08–2.41 (m, 10H), 2.40–1.70 (br, 2H), 2.20 (s, 3H), 1.88–1.72 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-[3-(1-propynyl)]-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8g}$. 39% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (t, J = 8 Hz, 1H), 7.2–7.1 (m, 3H), 5.77 (dd, J = 15, 7 Hz, 1H), 5.54 (dd, J = 15, 9 Hz, 1H), 4.42 (d, J = 6 Hz, 2H), 4.45–4.4 (m, 1H), 4.1–4.0 (m, 1H), 3.74 (s, 3H), 3.42 (m, 3H), 3.22 (s, 2H), 3.25–3.2 (m, 1H), 3.0–2.6 (m, 8H), 2.48 (dd, J = 18, 5 Hz, 1H), 2.19 (s, 3H), 1.9–1.8 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-[3-(2-phenylethynyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8h}$. 31% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.59–7.15 (m, 9H), 5.74 (dd, J = 15.6, 6.6 Hz, 1H), 5.54 (dd, J = 15.6, 8.2 Hz, 1H), 4.45–4.31 (m, 1H), 4.12–4.00 (m, 1H), 3.72 (s, 3H), 3.26–3.12 (m, 3H), 2.94–2.38 (m, 10H), 2.18 (s, 3H), 1.89–1.70 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-phenyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8i}$. 44% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64–7.15 (m, 9H), 5.75 (dd, J = 15.4, 6.6 Hz, 1H), 5.55 (dd, J = 15.4, 8.0 Hz, 1H), 4.48–4.32 (m, 1H), 4.12–4.00 (m, 1H), 3.72 (s, 3H), 3.26–3.12 (m, 3H), 2.98–2.38 (m, 10H), 2.17 (s, 3H), 1.88–1.66 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-[3-(2-thienyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8j}$. 44% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.42 (m, 2H), 7.34–7.23 (m, 3H), 7.17–7.09 (m, 1H), 7.06 (dd, J = 5.1, 3.3 Hz, 1H), 5.74 (dd, J = 15.3, 6.6 Hz, 1H), 5.55 (dd, J = 15.3, 8.2 Hz, 1H), 4.45–4.31 (m, 1H), 4.12–4.00 (m, 1H), 3.72 (s, 3H), 3.26–3.12 (m, 3H), 2.94–2.38 (m, 10H), 2.18 (s, 3H), 1.86–1.66 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-[3-(2-furyl)]phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8k}$. 40% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55–7.45 (m, 2H), 7.46 (d, J = 1.8 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.10 (m, 1H), 6.64 (d, J = 3.3 Hz), 6.46 (dd, J = 3.3, 1.8 Hz, 1H), 5.72 (dd, J = 15, 6.3 Hz, 1H), 5.55 (dd, J = 15, 8.0 Hz, 1H), 4.38 (m, 1H), 4.07 (m, 1H), 3.72 (s, 3H), 3.20 (s, 2H), 3.19 (m, 1H), 2.94–2.38 (m, 10H), 2.18 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-cyano)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8l}$. 31% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (t, J = 8 Hz, 1H), 7.2–7.1 (m, 3H), 5.77 (dd, J = 15, 7 Hz, 1H), 5.54 (dd, J = 15, 9 Hz, 1H), 4.42 (d, J = 6 Hz, 2H), 4.45–4.4 (m, 1H), 4.1–4.0 (m, 1H), 3.74 (s, 3H), 3.42 (m, 3H), 3.22 (s, 2H), 3.25–3.2 (m, 1H), 3.0–2.6 (m, 8H), 2.48 (dd, J = 18, 5 Hz, 1H), 2.19 (s, 3H), 1.9–1.8 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-trifluoromethyl)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 12-$_{8m}$. 44% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54–7.33 (m, 4H), 5.73 (dd, J = 15.4, 6.2 Hz, 1H), 5.55 (dd, J = 15.5, 7.8 Hz, 1H), 4.46–4.32 (m, 1H), 4.12–3.99 (m, 1H), 3.72 (s, 3H), 3.28–3.14 (m, 3H), 2.98–2.38 (m, 10H), 2.19 (s, 3H), 1.90–1.72 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3,4-dichloro)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14a}$. 37% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46–7.26 (m, 2H), 7.06 (dd, J = 8.4, 1.8 Hz, 1H), 5.70 (dd, J = 15.4, 6.4 Hz, 1H), 5.53 (dd, J = 15.4, 7.8 Hz, 1H), 4.46–4.24 (m, 1H), 4.18–3.98 (m, 1H), 3.73 (s, 3H), 3.32–3.14 (m, 3H), 3.00–2.34 (m, 10H), 2.19 (s, 3H), 1.92–1.70 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3,4-dimethoxy)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14b}$. 42% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.85–6.71 (m, 3H), 5.75 (dd, J = 15.6, 6.2 Hz, 1H) 5.57 (dd, J = 15.6, 8.0 Hz, 1H), 4.41–4.27 (m, 1H), 4.15–4.05 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H), 3.28–3.16 (m, 3H), 3.00–2.36 (m, 10H), 2.19 (s, 3H), 1.90–1.70 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-chloro-4-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14c}$. 39% yield in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.08 (dd, J = 8, 2 Hz, 1H), 6.86 (d, J = 8 Hz, 1H), 5.75 (dd, J = 16, 6 Hz, 1H), 5.56 (dd, J = 16, 8 Hz, 1H), 4.4–4.25 (m, 1H), 4.15–4.05 (m, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 3.3–3.2 (m, 1H), 3.23 (s, 2H), 2.95 (ddd, J = 17, 6, 2 Hz, 1H), 2.8–2.5 (m, 7H), 2.46 (dd, J = 17, 3 Hz, 1H), 2.38 (d, J = 7 Hz, 1H), 2.21 (s, 3H), 1.9–1.7 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methyl-4-methoxy)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14d}$. 44% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05–6.95 (m, 2H), 6.75 (d, J = 9.0 Hz, 1H), 5.75 (dd, J = 16, 6.0 Hz, 1H), 5.57 (dd, J = 16, 8.0 Hz, 1H), 4.31 (m, 1H), 4.10 (m, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.22 (s, 2H), 3.21 (m, 1H), 2.99–2.41 (m, 10H), 2.20 (s, 6H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methyl-4-hydroxy)-phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14e}$. 44% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95–6.85 (m, 2H), 6.67 (d, J = 8.0 Hz, 1H), 6.23 (s, 1H), 5.69 (dd, J = 15, 6.4 Hz, 1H), 5.52 (dd, J = 15, 8.3 Hz, 1H), 4.28 (m, 1H), 4.06 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.19 (m, 1H), 2.96–2.41 (m, 10H), 2.20 (s, 6H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-chloro-6-methoxyphenyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14f}$. 26% yield in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.4, 2.8 Hz, 1H), 7.12 (d, J = 2.8 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 5.72 (dd, J = 16, 6.3 Hz, 1H), 5.54 (dd, J = 16, 7.8 Hz, 1H), 4.41 (m, 1H), 4.08 (m, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.23 (s, 2H), 3.20 (m, 1H), 2.98–2.41 (m, 10H), 2.20 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(2,5-dimethylphenyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14g}$. 48% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.07–6.86 (m, 3H), 5.57 (dd, J = 15.4, 6.6 Hz, 1H), 5.58 (dd, J = 15.4, 8.4 Hz, 1H), 4.39–4.25 (m, 1H), 4.14–4.04 (m, 1H), 3.72 (s, 3H), 3.24–3.11 (m, 1H), 3.00–2.32 (m, 10H), 2.27 (s, 6H), 2.19 (s, 3H), 1.90–1.72 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(2-methoxy-3-methylphenyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14h}$. 50% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.1–6.95 (m, 3H), 5.73 (dd, J = 15, 6 Hz, 1H), 5.55 (dd, J = 15, 9 Hz, 1H), 4.5–4.4 (m, 1H), 4.1–4.0 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.22 (s, 2H), 3.25–3.15 (m, 1H), 3.0–2.5 (m, 8H), 2.32 (s, 3H), 2.20 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(2,3-dimethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14i}$. 46% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.09 (s, 4H), 5.74 (dd, J = 15, 6 Hz, 1H), 5.56 (dd, J = 15, 8 Hz, 1H), 4.35–4.3 (m, 1H), 4.1–4.05 (m, 1H), 3.70 (s, 3H), 3.22 (s, 2H), 3.25–3.2 (m, 1H), 2.92 (dd, J = 17, 7 Hz, 1H), 2.83 (dd, J = 14, 5 Hz, 1H), 2.8–2.6 (m, 4H), 2.57 (dt, J = 14, 8 Hz, 1H), 2.45 (dd, J = 17, 3 Hz, 1H), 2.30 (s, 3H), 2.16 (s, 3H), 1.9–1.8 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3,5-dimethyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14j}$. 46% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.92–6.72 (m, 3H), 5.73 (dd, J = 15.4, 6.2 Hz, 1H), 5.58 (dd, J = 15.4, 7.6 Hz, 1H), 4.40–4.24 (m, 1H), 4.15–4.03 (m, 1H), 3.73 (s, 3H), 3.27–3.14 (m, 1H), 2.97–2.38 (m, 10H), 2.28 (s, 6H), 2.19 (s, 3H), 1.90–1.72 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-methoxy-5-methyl)phenyl-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{14k}$. 44% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.15 (m, 1H), 6.8–6.7 (m, 3H), 5.77 (dd, J = 15, 6 Hz, 1H), 5.57 (dd, J = 15, 8 Hz, 1H), 4.4–4.3 (m, 1H), 4.15–4.0 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.22 (s, 2H), 3.3–3.2 (m, 1H), 3.0–2.4 (m, 9H), 2.20 (s, 3H), 1.9–1.7 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(2-naphtyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{15a}$. 45% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84–7.30 (m, 7H), 5.77 (dd, 1H, J = 15.4, 6.2 Hz), 5.54 (dd, 1H, J = 15.4, 8.0 Hz), 4.54–4.38 (m, 1H), 4.10–3.98 (m, 1H), 3.71 (s, 3H), 3.24–3.14 (m, 3H), 3.00 (d, J = 6.6 Hz, 2H), 2.93–2.30 (m, 8H), 2.18 (s, 3H), 1.81–1.63 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(5-isocoumaranyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{15b}$. 41% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2–7.0 (m, 3H), 5.74 (dd, J = 15, 6.4 Hz, 1H), 5.55 (dd, J = 15, 8.2 Hz, 1H), 5.07 (s, 4H), 4.35 (m, 1H), 4.08 (m, 1H), 3.73 (s, 3H), 3.22 (s, 2H), 3.21 (m, 1H), 2.97–2.39 (m, 10H), 2.20 (s, 3H), 1.9–1.7 (m, 2H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(3-thienyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{15c}$. 39% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.2 (m, 1H), 7.06 (d, J = 2 Hz, 1H), 6.99 (dd, J = 5, 2 Hz, 1H), 5.76 (dd, J = 15, 6 Hz, 1H), 5.58 (dd, J = 15, 8 Hz, 1H), 4.45–4.3 (m, 1H), 4.15–4.05 (m, 1H), 3.73 (s, 3H), 3.3–3.2 (m, 1H), 3.22 (s, 2H), 3.0–2.4 (m, 9H), 2.20 (s, 3H), 1.9–1.7 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-(2-thienyl)-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{15d}$. 46% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16 (dd, J = 5.2, 1.2 Hz, 1H), 6.94 (dd, J = 5.2, 3.4 Hz, 1H), 6.89–6.84 (m, 1H), 5.75 (dd, J = 15.4, 5.6 Hz, 1H), 5.61 (dd, J = 15.4, 7.8 Hz, 1H), 4.44–4.30 (m, 1H), 4.16–4.03 (m, 1H), 3.73 (s, 3H), 3.28–3.17 (m, 3H), 3.17–2.24 (m, 10H), 2.19 (s, 3H), 1.92–1.72 (m, 3H).

Methyl 9-acetoxy-11,15-dihydroxy-16-[3-(5-methoxymethyl)thienyl]-ω-tetranor-3,7-dithiaprosta-8,13-dienoate 17-$_{15e}$. 22% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.08 (dd, J = 8, 2 Hz, 1H), 6.86 (d, J = 8 Hz, 1H),

5.75 (dd, $J=16$, 6 Hz, 1H), 5.56 (dd, $J=16$, 8 Hz, 1H), 4.4–4.25 (m, 1H), 4.15–4.05 (m, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 3.3–3.2 (m, 1H), 3.23 (s, 3H), 2.95 (ddd, $J=17$, 6, 2 Hz, 1H), 2.8–2.5 (m, 7H), 2.46 (dd, $J=17$, 3 Hz, 1H), 2.38 (d, $J=7$ Hz, 1H), 2.21 (s, 3H), 1.9–1.7 (m, 3H).

16-(2-Methyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6a}$. A mixture of **12-$_{6a}$** (32 mg, 0.063 mmol) and Amano PS (100 mg) in dimethylsulfoxide (2 mL) and phosphate buffer (pH7.4, 2 mL) was vigorously stirred for 3 h at room temperature. After the hydrolysis was completed, porcine liver esterase (PLE, Sigma, 20,000 U, 0.1 mL) was added and the mixture was stirred for an additional 1 h. The resulting mixture was poured into saturated aqueous $(NH_4)_2SO_4$ and shaken with EtOAc. The insoluble substances were removed by filtration through a pad of Celite. The filtrate was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 3/1 to EtOAc/AcOH, 50/1) to afford **13-$_{6a}$** as a colorless oil (23 mg, 83%). IR (neat) 3600–3200, 2922, 1732, 1494, 1417, 1261, 1151, 1082, 973, 850, 747, 669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21–7.10 (m, 4H), 5.95–5.56 (m, 2H), 4.56–4.36 (m, 1H), 4.20–4.00 (m, 1H), 3.40–2.26 (1m, 8H), 1.98–1.78 (m, 2H); MS (APCI) m/z 423 $(M-H)^-$.

16-(3-Methyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6b}$. 87% yield; IR (neat) 3391, 2919, 2248, 1731, 1609, 1488, 1417, 1266, 1147, 1081, 1036, 971, 911, 786, 734, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.0 (m, 4H), 5.9–5.5 (m, 2H), 4.5–4.0 (m, 2H), 3.8–3.6 (br), 3.22 (s, 2H), 3.4–2.2 (m, 10H), 2.33 (s, 3H), 2.0–1.8 (m, 2H); MS (APCI) m/z 423 $(M-H)^-$.

16-(4-Methyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6c}$. 85% yield; IR (neat) 3392, 2920, 1729, 1417, 1263, 1115, 910, 806, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2–7.0 (m, 4H), 5.84 (dd, $J=15$, 5 Hz, 1H), 5.63 (dd, $J=15$, 8 Hz, 1H), 4.5–4.3 (m, 1H), 4.2–4.0 (m, 1H), 3.5–2.8 (br), 3.21 (s, 2H), 3.4–3.3 and 3.0–2.3 (m, 10H), 2.32 (s, 3H), 2.0–1.8 (m, 2H); MS (EI) m/z 406 $(M-H_2O)^+$.

16-(3-Chloro)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6d}$. 90% yield; IR (neat) 3392, 2920, 2650, 2250, 1731, 1599, 1574, 1478, 1429, 1262, 1147, 1081, 1029, 971, 910, 784, 731, 704, 685, 649 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.0 (m, 4H), 5.9–5.5 (m, 2H), 4.44 (m, 1H), 4.07 (m, 1H), 3.6–3.4 (br), 3.23 (s, 2H), 3.4–2.2 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 443 $(M-H)^-$.

16-(4-Chloro)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6e}$. 51% yield; IR (neat) 3391, 2922, 1730, 1408, 1271, 1087, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (d, $J=8$ Hz, 2H), 7.16 (d, $J=8$ Hz, 2H), 5.9–5.7 (m, 1H), 5.62 (dd, $J=15$, 8 Hz, 1H), 4.5–4.4 (m, 1H), 4.2–4.0 (m, 1H), 3.22 (s, 2H), 3.4–2.8 (br), 3.4–3.3 and 3.0–2.3 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 443 $(M-H)^-$.

16-(2-Methoxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6f}$. 51% yield; IR (neat) 3600–3200, 2919, 1730, 1494, 1439, 1245, 1119, 1083, 1025, 759 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.08 (m, 2H), 7.00–6.85 (m, 2H), 5.87–5.52 (m, 2H), 4.68–3.90 (m, 2H), 3.87 (s, 3H), 3.66–2.12 (1m, 5H), 1.98–1.78 (m, 2H); MS (APCI) m/z 439 $(M-H)^-$.

16-(3-Methoxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6g}$. 70% yield; IR (neat) 3402, 2921, 1733, 1602, 1490, 1437, 1260, 1153, 1081, 1042, 971, 912, 785, 735, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.2 (m, 1H), 6.85–6.75 (m, 3H), 5.9–5.75 (m, 1H), 5.61 (dd, $J=15$, 8 Hz, 1H), 4.5–4.3 and 4.1–3.9 (m, 2H), 3.79 (s, 3H), 3.7–3.2 (br), 3.22 (s, 2H), 3.4–3.3 and 3.0–2.2 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 439 $(M-H)^-$.

16-(4-Methoxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6h}$. 72% yield; IR (neat) 3392, 2917, 1732, 1514, 1246, 1083, 1032, 826, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.15 (d, $J=8$ Hz, 2H), 6.86 (d, $J=8$ Hz, 2H), 5.9–5.75 (m, 1H), 5.62 (ss, $J=16$, 8 Hz, 1H), 4.5–4.3 and 4.2–4.0 (m, 2H), 3.22 (s, 2H), 3.4–2.7 (br), 3.4–3.3 and 3.0–2.3 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 439 $(M-H)^-$.

16-(3-Ethoxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6i}$. 66% yield; IR (neat) 3392, 2926, 1732, 1601, 1584, 1489, 1257, 1050 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27–7.17 (m, 1H), 6.80–6.76 (m, 3H), 5.87–5.53 (m, 2H), 4.80–4.40 (br, 4H), 4.14–4.00 (m, 1H), 4.02 (q, $J=7.0$ Hz, 2H), 3.38–2.18 (m, 10H), 3.22 (s, 2H), 1.92–1.78 (m, 2H), 1.41 (t, $J=7.0$ Hz, 3H); MS (APCI) m/z 453 $(M-H)^-$.

16-(4-Ethoxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6j}$. 95% yield; IR (neat) 3392, 2919, 1732, 1613, 1583, 1511, 1299, 1245, 1047 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12 (d, $J=8.8$ Hz, 2H), 6.84 (d, $J=8.8$ Hz, 2H), 5.87–5.54 (m, 2H), 4.46–4.32 (m, 1H), 4.40–3.65 (4H, br), 4.01 (2H, q, $J=7.0$ Hz), 3.39–2.20 (m, 10H), 3.22 (s, 2H), 1.94–1.80 (m, 2H), 1.40 (t, $J=7.0$ Hz, 3H); MS (APCI) m/z 453 $(M-H)^-$.

16-(3-Methylthio)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6k}$. 96% yield; IR (neat) 3392, 2921, 1732, 1593, 1573, 1476, 1421, 1266, 1147, 1084, 1028, 970, 909, 783, 730, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (m, 1H), 7.12 (m, 2H), 6.99, (m, 1H), 5.9–5.5 (m, 2H), 4.43 (m, 1H), 4.03 (m, 1H), 4.0–3.6 (br), 3.22 (s, 2H), 3.4–2.1 (m, 10H), 2.48 (s, 3H), 2.0–1.8 (m, 2H); MS (APCI) m/z 455 $(M-H)^-$.

16-(4-Methylthio)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6l}$. 96% yield; IR (neat) 3391, 2920, 1731, 1495, 1417, 1266, 1148, 1085, 1027, 970, 911, 805, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22 (d, $J=9$ Hz, 2H), 7.14 (d, $J=9$ Hz, 2H), 5.9–5.55 (m, 2H), 4.43 (m, 1H), 4.06 (m, 1H), 3.22 (s, 2H), 3.4–2.2 (m, 13H), 2.47 (s, 3H), 2.0–1.8 (m, 2H); MS (APCI) m/z 455 $(M-H)^-$.

16-(3-Hydroxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6m}$. 49% yield; IR (neat) 3600-3200, 2985, 2936, 1736, 1589, 1455, 1375, 1245, 1158, 1046, 849, 787, 699, 636, 610 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 7.15–7.02

(m, 1H), 6.78–6.56 (m, 3H), 5.74 (dd, $J=15.4$, 5.8 Hz, 1H), 5.67–5.51 (m, 1H), 4.38–4.23 (m, 1H), 4.11–3.95 (m, 1H), 3.50–2.06 (m, 2H), 1.97–1.72 (m, 2H); MS (APCI) m/z 425 $(M-H)^-$.

16-(4-Hydroxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6n}$. 48% yield; IR (neat) 3368, 2919, 1730, 1614, 1515, 1445, 1245 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05 (d, $J=8.4$ Hz, 2H), 6.69 (d, $J=8.4$ Hz, 2H), 5.73 (dd, $J=15.4$, 6.2 Hz, 1H), 5.56 (dd, $J=15.4$, 7.4 Hz, 1H), 4.95–4.80 (4H, br), 4.38–4.19 (m, 1H), 4.10–3.98 (m, 1H), 3.48–2.15 (m, 10H), 3.22 (s, 2H), 1.91–1.78 (m, 2H); MS (APCI) m/z 425 $(M-H)^-$.

16-(3-Methylsulfonyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6o}$. 44% yield; IR (neat) 3391, 2924, 1732, 1417, 1296, 1143 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85–7.76 (m, 2H), 7.64–7.50 (m, 2H), 5.83–5.50 (m, 2H), 4.43–3.99 (m, 2H), 3.49–2.12 (m, 10H), 3.22 (s, 2H), 3.12 (s, 3H), 1.93–1.78 (m, 2H); MS (APCI) m/z 487 $(M-H)^-$.

16-(4-Methylsulfonyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6p}$. 79% yield; IR (neat) 3418, 2924, 2639, 1732, 1598, 1411, 1295, 1147, 1088, 1035, 966, 766, 669, 534 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.52 (m, 2H), 5.69 (m, 2H), 4.36 (m, 1H) 4.05 (m, 1H), 3.52–2.08 (m, 10H), 3.23 (s, 2H), 3.10 (s, 3H), 2.0–1.8 (m, 2H); MS (APCI) m/z 487 $(M-H)^-$.

16-(3-Methoxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6q}$. 72% yield; IR (neat) 3392, 2922, 1730, 1265, 1193, 1157, 1084, 971, 912, 732, 705 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.10 (m, 4H), 5.9–5.5 (m, 2H), 4.6–4.4 (m, 3H), 4.43 (s, 2H), 4.4–4.3 and 4.05–3.9 (m, 1H), 3.8–3.1 (br, 3H), 3.42 and 3.41 (s, 3H), 3.22 (s, 2H), 3.4–3.3 and 3.0–2.2 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 453 $(M-H)^-$.

16-(4-Methoxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{6r}$. 75% yield; IR (neat) 3392, 2921, 1732, 1417, 1270, 1084, 971, 911, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.15 (m, 4H), 5.9–5.5 (m, 2H), 4.5–4.4 (m, 3H), 4.4–4.3 and 4.1–3.9 (m, 1H), 4.0–3.5 (br, 3H), 3.42 (m, 3H), 3.22 (s, 2H), 3.4–3.3 and 3.0–2.2 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 453 $(M-H)^-$.

16-(3-Hydroxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7a}$. 49% yield; IR (neat) 3392, 2921, 1732, 1417, 1261, 1153, 1082, 1040, 901, 792, 705 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31–7.09 (m, 4H), 5.75 (dd, $J=15$, 6.2 Hz, 1H), 5.59 (dd, $J=15$, 7.3 Hz, 1H), 4.58 (s, 2H), 4.32 (m, 1H), 4.02 (m, 1H), 3.22 (s, 2H), 3.49–2.08 (m, 10H), 1.9–1.7 (m, 2H); MS (APCI) m/z 439 $(M-H)^-$.

16-(3-Methylthiomethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7b}$. 76% yield; IR (neat) 3600–3200, 2917, 1732, 1424, 1375, 1249, 1148, 1083, 1046, 972, 757, 707 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.05 (m, 4H), 5.92–5.56 (m, 2H), 4.58–3.96 (m, 2H), 3.88–2.10 (1m, 7H), 2.04–2.02 (m, 3H), 1.98–1.78 (m, 2H); MS (APCI) m/z 469 $(M-H)^-$.

16-(3-Methoxyethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7c}$. 87% yield; IR (neat) 3392, 2921, 1732, 1608, 1488, 1446, 1265, 1084 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.01 (m, 4H), 5.80 (dd, $J=15.4$, 5.8 Hz, 1H), 5.60 (dd, $J=15.4$, 8.0 Hz, 1H), 5.50–4.60 (br, 3H), 4.47–4.28 (m, 1H), 4.06–3.96 (m, 1H), 3.65 (t, $J=6.6$ Hz, 2H), 3.35 (s, 3H), 3.21 (s, 2H), 3.00–2.18 (1m, 2H), 1.93–1.80 (m, 2H); MS (APCI) m/z 467 $(M-H)^-$.

16-(3-Methoxypropyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7d}$. 73% yield; IR (neat) 3600–3200, 2923, 1732, 1608, 1446, 1417, 1255, 1083, 1046, 971, 757, 706, 667 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–6.97 (m, 4H), 5.90–5.68 (m, 1H), 5.60 (dd, $J=15.4$, 8.0 Hz, 1H), 5.50–5.00 (br, 3H), 4.52–4.28 (m, 1H), 4.13–3.94 (m, 1H), 3.42 (t, $J=6.4$ Hz, 2H), 3.35 (s, 3H), 3.21 (s, 2H), 3.04–2.13 (1m, 2H), 1.99–1.76 (m, 4H); MS (APCI) m/z 481$(M-H)^-$.

16-(3-Ethoxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7e}$. 56% yield; IR (neat) 3600-3200, 2976, 2927, 1732, 1445, 1417, 1375, 1250, 1158, 1084, 1046, 972, 757, 705, 667 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.10 (m, 4H), 5.91–5.47 (m, 2H), 4.60–3.50 (m, 9H), 3.38–2.10 (1m, 2H), 1.96–1.76 (m, 2H), 1.25 (3H, t, $J=6.9$ Hz); MS (APCI) m/z 467 $(M-H)^-$.

16-(3-Propoxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7f}$. 88% yield; IR (neat) 3392, 2927, 2874, 1733, 1417, 1362, 1262, 1157, 1083, 1038, 970, 910, 772, 733, 705 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37–7.10 (m, 4H), 5.89–5.48 (m, 2H), 4.58–3.87 (m, 2H), 4.48 (s, 2H), 4.42 (3H, br), 3.49 (t, $J=7$ Hz, 2H), 3.21 (s, 2H), 3.38–2.14 (m, 10H), 1.9–1.7 (m, 2H), 1.7–1.6 (m, 2H), 0.94 (t, $J=7$ Hz, 3H); MS (APCI) m/z 481 $(M-H)^-$.

16-(3-Allyloxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7g}$. 79% yield; IR (neat) 3600-3200, 2921, 1732, 1418, 1347, 1265, 1157, 1080, 933, 793, 758, 705 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37–7.09 (m, 4H), 6.07–5.18 (m, 8H), 4.62–3.86 (m, 6H), 3.40–2.12 (1m, 2H), 1.96–1.74 (m, 2H); MS (APCI) m/z 479 $(M-H)^-$.

16-(3-Isopropoxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7h}$. 72% yield; IR (neat) 3392, 2927, 1733, 1383, 1262, 1125, 1073, 912, 793, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 5.9–5.5 (m, 2H), 4.6–4.4 (m, 3H), 4.4–4.25 and 4.0–3.9 (m, 1H), 3.85–3.65 (m, 1H), 3.6–3.2 (br, 3H), 3.22 (s, 2H), 3.4–3.3 and 3.0–2.2 (m, 10H), 2.0–1.8 (m, 2H), 1.3–1.2 (m, 6H); MS (APCI) m/z 481 $(M-H)^-$.

16-(3-Phenoxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7i}$. 85% yield; IR (neat) 3392, 2921, 1731, 1599, 1494, 1383, 1240, 1080, 1035, 792, 758, 695 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.13 (m, 6H), 6.97 (m, 3H), 5.88–5.52 (m, 2H), 5.03 (s, 2H), 4.53–3.90 (m, 2H), 4.6–4.2 (br), 3.20 (s, 2H), 3.38–2.12 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 515 $(M-H)^-$.

16-(3-Cyclohexyloxymethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7j}$. 81% yield; IR (neat) 3600–3200, 2932, 2857, 1732, 1449, 1374, 1246, 1155, 1082, 970, 791, 757,

705, 667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34–7.08 (m, 4H), 5.90–5.46 (m, 2H), 5.10–4.60 (br, 3H), 4.60–3.70 (m, 4H), 3.50–3.28 (m, 1H), 3.20 (s, 2H), 3.14–2.24 (m, 10H), 2.10–1.10 (1m, 2H); MS (APCI) *m/z* 521 $(M-H)^-$

16-[3-(1-Methoxyethyl)]phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{7k}$. 78% yield; IR (neat) 3392, 2927, 1731, 1446, 1261, 1083, 913, 797, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35–7.1 (m, 4H), 5.9–5.5 (m, 2H), 4.65–4.45 (m, 1H), 4.4–4.25 (m, 1H), 4.1–3.9 (m, 1H), 4.2–3.4 (br, 3H), 3.27 and 3.26 (s, 3H), 3.22 (s, 2H), 3.4–3.3 and 3.05–2.3 (m, 8H), 2.0–1.8 (m, 2H), 1.45 (d, $J=7$ Hz, 3H); MS (APCI) *m/z* 467 $(M-H)^-$.

16-(3-Ethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8a}$. 36% yield; IR (neat) 3600–3200, 2964, 2928, 1731, 1607, 1488, 1417, 1375, 1255, 1148, 1082, 1046, 971, 798, 757, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30–6.96 (m, 4H), 5.90–5.55 (m, 2H), 4.43–4.30 (m, 1H), 4.14–3.96 (m, 1H), 3.90–3.41 (br, 3H), 3.41–2.16 (m, 4H), 1.96–1.78 (m, 2H), 1.23 (t, $J=7.5$ Hz, 3H); MS (APCI) *m/z* 437 $(M-H)^-$.

16-(3-Vinyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8b}$. 55% yield; IR (neat) 3600–3200, 2984, 2927, 1732, 1375, 1245, 1153, 1082, 1046, 972, 912, 800, 758, 717 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.37–7.05 (m, 4H), 6.68 (1H, dd, $J=17.8$, 10.8 Hz), 5.92–5.50 (m, 3H), 5.44–4.70 (m, 4H), 4.54–3.92 (m, 2H), 3.40–2.10 (m, 2H), 1.96–1.74 (m, 2H); MS (APCI) *m/z* 435 $(M-H)^-$.

16-(3-Propyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8c}$. 80% yield; IR (neat) 3392, 2928, 1732, 1417, 1261, 1080, 909, 787, 732, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.3–7.0 (m, 4H), 5.9–5.6 (m, 2H), 4.55–4.3 and 4.1–4.0 (m, 1H), 3.6–3.0 (br, 3H), 3.22 (s, 2H), 3.4–3.3 and 3.0–2.2 (m, 12H), 2.0–1.8 (m, 2H), 1.75–1.55 (m, 2H), 0.94 (t, $J=7$ Hz, 3H); MS (APCI) *m/z* 451 $(M-H)^-$.

16-(3-Isopropyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8d}$. 78% yield; IR (neat) 3392, 2960, 1733, 1418, 1262, 1082, 970, 912, 794, 731, 707 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.3–7.0 (m, 4H), 5.9–5.6 (m, 2H), 4.55–4.4 and 4.2–4.0 (m, 2H), 4.2–3.8 (br, 3H), 3.22 (s, 2H), 3.4–3.3 and 3.0–2.2 (m, 11H), 2.0–1.8 (m, 2H), 1.24 (d, $J=7$ Hz, 6H); MS (APCI) *m/z* 451 $(M-H)^-$.

16-(3-Benzyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8e}$. 47% yield; IR (neat) 3391, 3026, 2919, 1732, 1601, 1494, 1445, 1265, 1147, 1077, 1030, 970, 910, 733, 707 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34–6.99 (m, 9H), 5.84–5.49 (m, 2H), 5.0–4.6 (br), 4.39 (m, 1H), 3.97 (m, 1H), 3.94 (s, 2H), 3.19 (s, 2H), 3.37–2.22 (m, 10H), 1.9–1.7 (m, 2H); MS (APCI) *m/z* 499 $(M-H)^-$.

16-[3-(2-Fluoroethyl)]phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8f}$. 88% yield; IR (neat) 3392, 2918, 1732, 1609, 1489, 1417, 1261, 1148, 1080 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.04 (m, 4H), 5.79 (dd, $J=15.4$, 6.2 Hz, 1H), 5.59 (dd, $J=15.4$, 8.2 Hz, 1H), 5.50–4.90 (br, 3H), 4.62 (dt, $J=7.0$ Hz, 2H), 4.47–4.29 (m, 1H), 4.10–3.96 (m, 1H), 3.21 (s, 2H), 3.07–2.20 (m, 2H), 1.92–1.89–1.69 (m, 2H); MS (APCI) *m/z* 455 $(M-H)^-$.

16-[3-(1-Propynyl)]phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8g}$. 74% yield; IR (neat) 3392, 2917, 1728, 1418, 1265, 1147, 1081, 971, 910, 793, 731 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 4H), 5.9–5.5 (m, 2H), 4.5–4.35 and 4.1–4.0 (m, 2H), 3.9–3.2 (br, 3H), 3.22 (s, 2H), 3.4–3.3 and 3.0–2.3 (m, 10H), 2.04 (s, 3H), 2.0–1.8 (m, 2H); MS (APCI) *m/z* 447 $(M-H)^-$.

16-[3-(2-Phenylethynyl)]phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8h}$. 81% yield; IR (neat) 3600–3200, 2922, 1732, 1602, 1494, 1443, 1418, 1278, 1217, 1148, 1082, 1027, 971, 757, 692, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.11 (m, 9H), 5.89–5.67 (m, 1H), 5.57 (dd, $J=15.4$, 8.0 Hz, 1H), 4.94–4.30 (m, 4H), 4.12–3.93 (m, 1H), 3.42–2.12 (1m, 2H), 1.95–1.72 (m, 2H); MS (APCI) *m/z* 509 $(M-H)^-$.

16-(3-Phenyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8i}$. 63% yield; IR (neat) 3600-3200, 2921, 1731, 1715, 1600, 1481, 1417, 1374, 1256, 1153, 1078, 1046, 972, 760, 729, 703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.64–7.14 (m, 9H), 5.95–5.57 (m, 2H), 4.64–3.92 (m, 2H), 3.40–2.08 (1m, 5H), 1.96–1.74 (m, 2H); MS (APCI) *m/z* 485 $(M-H)^-$.

16-[3-(2-Thienyl)]phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8j}$. 51% yield; IR (neat) 3600–3200, 2922, 1732, 1605, 1483, 1443, 1424, 1375, 1251, 1148, 1082, 1046, 971, 789, 757, 703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55–7.40 (m, 2H), 7.36–7.22 (m, 3H), 7.15–7.02 (m, 2H), 5.88–5.69 (m, 1H), 5.56 (dd, $J=15.4$, 8.0 Hz, 1H), 5.14–4.55 (br, 3H), 4.50–4.27 (m, 1H), 4.09–3.90 (m, 1H), 3.37–2.12 (m, 2H), 1.92–1.70 (m, 2H); MS (APCI) *m/z* 491 $(M-H)^-$.

16-[3-(2-Furyl)]phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8k}$. 90% yield; IR (neat) 3398, 2920, 2361, 1731, 1611, 1419, 1289, 1154, 1079, 1015, 910, 791, 734, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.6–7.5 (m, 2H), 7.47 (d, $J=1.9$ Hz, 1H), 7.32 (t, $J=7.9$ Hz, 1H), 7.10 (d, $J=7.9$ Hz, 1H), 6.66 (d, $J=3.4$ Hz, 1H), 6.47 (dd, $J=3.4$, 1.9 Hz, 1H), 5.91–5.53 (m, 2H), 4.56–3.94 (m, 2H), 4.0–3.6 (br), 3.21 (s, 2H), 3.39–2.13 (m, 10H), 1.9–1.7 (m, 2H); MS (APCI) *m/z* 475 $(M-H)^-$.

16-(3-Cyano)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8l}$. 61% yield; IR (neat) 3413, 2924, 2230, 1730, 1417, 1265, 1149, 1081, 1031, 972, 913, 732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.6–7.4 (m, 4H), 5.85–5.5 (m, 2H), 4.45–4.3 and 4.1–3.95 (m, 2H), 3.22 (s, 2H), 3.4–3.35 and 3.0–2.2 (m, 13H), 2.0–1.8 (m, 2H); MS (APCI) *m/z* 434 $(M-H)^-$.

16-(3-Trifluoromethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 13-$_{8m}$. 73% yield; IR (neat) 3600–3200, 2927, 1732, 1450, 1376, 1331, 1251, 1163, 1124, 1075, 1046, 971, 801, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.57–7.38 (m, 4H), 5.91–5.57 (m, 2H), 4.54–3.98 (m, 2H), 3.46–2.14 (1m, 5H), 1.97–1.78 (m, 2H); MS (APCI) *m/z* 477 $(M-H)^-$.

16-(3,4-Dichloro)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14a}$. 77% yield; IR (neat) 3600–3200, 2927, 1731, 1713, 1472, 1395, 1260, 1133, 1082, 1032, 972, 896, 820 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 1.8 Hz, 1H), 7.07 (dd, J = 8.4, 1.8 Hz, 1H), 5.92–5.54 (m, 2H), 4.53–4.32 (m, 1H), 4.20–4.00 (m, 1H), 3.44–2.12 (1m, 5H), 1.98–1.80 (m, 2H); MS (APCI) m/z 477 (M−H)$^-$.

16-(3,4-Dimethoxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14b}$. 29% yield; IR (neat) 3600–3200, 2932, 1732, 1516, 1465, 1418, 1261, 1141, 1029, 809, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.88–6.72 (m, 3H), 5.93–5.58 (m, 2H), 4.54–4.00 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.60–2.16 (1m, 5H), 1.98–1.78 (m, 2H); MS (APCI) m/z 469 (M−H)$^-$.

16-(3-Chloro-4-methoxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14c}$. 72% yield; IR (neat) 3392, 2920, 1732, 1504, 1441, 1257, 1148, 1065, 1024, 972, 908, 811, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (d, J = 2 Hz, 1H), 7.08 (dd, J = 8, 2 Hz, 1H), 6.88 (d, J = 8 Hz, 1H), 5.81 and 5.79 (dd, J = 15, 5 Hz, 1H), 5.72 and 5.62 (dd, J = 15, 8 Hz, 1H), 4.45–4.4 and 4.1–4.05 (m, 2H), 3.89 (s, 3H), 3.7–2.8 (br, 3H), 3.22 (s, 3H), 3.38 and 3.0–2.5 (m, 9H), 2.42 (dd, J = 19, 10 Hz), 2.26 (dd, J = 19, 7 Hz), 1.9–1.8 (m, 2H); MS (APCI) m/z 473 (M−H)$^-$.

16-(3-Methyl-4-methoxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14d}$. 84% yield; IR (neat) 3392, 2919, 2248, 1732, 1614, 1505, 1417, 1253, 1226, 1135, 1081, 1035, 972, 911, 811, 733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05–6.95 (m, 2H), 6.76 (d, J = 9.0 Hz, 1H), 5.90–5.55 (m, 2H), 4.40 (m, 1H), 4.06 (m, 1H), 4.3–3.7 (br), 3.81 (s, 3H), 3.21 (s, 2H), 3.41–2.27 (m, 10H), 2.20 (s, 3H), 2.0–1.8 (m, 2H); MS (APCI) m/z 453 (M−H)$^-$.

16-(3-Methyl-4-hydroxy)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14e}$. 72% yield; IR (neat) 3392, 2920, 1732, 1715, 1614, 1509, 1423, 1265, 1151, 1120, 1081, 1043, 972, 820, 782 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 6.9–6.8 (m, 2H), 6.64 (d, J = 8.0 Hz, 1H), 5.72 (dd, J = 15, 6.2 Hz, 1H), 5.56 (dd, J = 15, 7.8 Hz, 1H), 4.37–3.95 (m, 2H), 3.22 (s, 2H), 3.48–2.13 (m, 10H), 2.15 (s, 3H), 1.9–1.7 (m, 2H); MS (APCI) m/z 439 (M−H)$^-$.

16-(3-Chloro-6-methoxyphenyl)-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14f}$. 93% yield; IR (neat) 3392, 2921, 1732, 1489, 1248, 1130, 1081, 1029, 970, 910, 809, 773, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2–7.1 (m, 2H), 6.82 (d, J = 8.8 Hz, 1H), 5.87–5.54 (m, 2H), 4.62–3.95 (m, 2H), 3.84 (s, 3H), 3.7–3.3 (br), 3.22 (s, 2H), 3.37–2.17 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 473 (M−H)$^-$.

16-(2,5-Dimethylphenyl)-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14g}$. 18% yield; IR (neat) 3600–3200, 2923, 1733, 1504, 1417, 1261, 1147, 1081, 1040, 971, 813, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12–6.88 (m, 3H), 5.93–5.56 (m, 2H), 4.52–3.80 (m, 5H), 3.42–2.14 (1m, 8H), 1.98–1.78 (m, 2H); MS (APCI) m/z 437 (M−H)$^-$.

16-(2-Methoxy-3-methylphenyl)-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14h}$. 63% yield; IR (neat) 3402, 2926, 1730, 1471, 1422, 1259, 1213, 1167, 1089, 1008, 911, 771, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2–7.0 (m, 3H), 5.76 (dd, J = 16, 5 Hz, 1H), 5.52 (dd, J = 16, 8 Hz, 1H), 4.7–4.5 (m, 1H), 4.3–4.2 and 4.0–3.8 (m, 1H), 4.4–3.4 (br, 3H), 3.78 (s, 3H), 3.22 (s, 2H), 3.3–3.2 and 3.1–2.3 (m, 10H), 2.30 (s, 3H), 1.95–1.8 (m, 2H); MS (APCI) m/z 453 (M−H)$^-$.

16-(2,3-Dimethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14i}$. 83% yield; IR (neat) 3392, 2921, 1731, 1261, 1077, 910, 781, 730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.1–7.0 (m, 3H), 5.9–5.6 (m, 2H), 4.5–4.4 (m, 1H), 4.2–4.0 (m, 1H), 3.8–3.0 (br, 3H), 3.22 (s, 2H), 3.4–3.35 and 3.0–2.3 (m, 10H), 2.28 (s, 3H), 2.24 (s, 3H), 2.0–1.8 (m, 2H); MS (APCI) m/z 437 (M−H)$^-$.

16-(3,5-Dimethyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14j}$. 37% yield; IR (neat) 3600–3200, 2919, 1730, 1606, 1417, 1294, 1148, 1083, 1037, 971, 842, 757, 710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.88 (brs, 1H), 6.83 (br2, 2H), 5.91–5.58 (m, 2H), 4.55–4.30 (m, 1H), 4.16–3.96 (m, 1H), 3.42–2.32 (m, 5H), 2.29 (s, 6H), 1.99–1.78 (m, 2H); MS (APCI) m/z 437 (M−H)$^-$.

16-(3-Methoxy-5-methyl)phenyl-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{14k}$. 85% yield; IR (neat) 3392, 2920, 1736, 1596, 1460, 1294, 1153, 1069, 970, 912, 836, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.65–6.55 (m, 3H), 5.9–5.6 (m, 2H), 4.5–4.3 and 4.1–4.0 (m, 2H), 3.79 (s, 3H), 3.7–3.0 (br, 3H), 3.22 (s, 2H), 3.4–3.3 and 3.0–2.3 (m, 10H), 2.32 (s, 3H), 2.0–1.8 (m, 2H); MS (APCI) m/z 453 (M−H)$^-$.

16-(2-Naphthyl)-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{15a}$. 37% yield; IR (neat) 3600–3200, 2927, 1732, 1715, 1374, 1246, 1078, 1046, 971, 820, 754, 735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.87–7.28 (m, 7H), 5.96–5.46 (m, 2H), 4.66–3.88 (m, 2H), 3.60–2.10 (1m, 5H), 1.92–1.70 (m, 2H); MS (APCI) m/z 459 (M−H)$^-$.

16-(5-Isocoumaranyl)-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{15b}$. 82% yield; IR (neat) 3391, 2917, 2649, 2359, 1731, 1715, 1494, 1417, 1372, 1260, 1143, 1082, 1044, 972, 892, 822, 775, 707 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2–7.0 (m, 3H), 5.73 (dd, J = 15, 6.3 Hz, 1H), 5.58 (dd, J = 15, 7.6 Hz, 1H), 5.04 (s, 4H), 4.30 (m, 1H) 4.04 (m, 1H), 3.21 (s, 2H), 3.50–2.16 (m, 10H), 1.9–1.8 (m, 2H); MS (APCI) m/z 451 (M−H)$^-$.

16-(3-Thienyl)-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{15c}$. 75% yield; IR (neat) 3392, 2918, 1732, 1417, 1262, 1147, 1080, 971, 911, 781, 730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (dd, J = 5, 2 Hz, 1H), 7.08 (d, J = 2 Hz, 1H), 6.98 (d, J = 5 Hz, 1H), 5.9–5.75 (m, 1H), 5.65 (dd, J = 15, 8 Hz, 1H), 4.55–4.4 (m, 1H), 4.45–4.3 and 4.15–4.0 (m, 1H), 3.22 (s, 2H), 3.4–3.35 and 3.2–2.2 (m, 13H), 2.0–1.8 (m, 2H); MS (APCI) m/z 415 (M−H)$^-$.

16-(2-Thienyl)-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{15d}$. 73% yield; IR (neat) 3600–3200, 2917, 1730, 1715, 1417, 1298, 1082, 1039, 851, 703 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19 (dd, J = 5.1, 1.2 Hz, 1H), 6.97 (dd, J = 5.1, 3.3 Hz, 1H), 6.92–6.85 (m, 1H), 5.91–5.58 (m, 2H),

4.58–4.32 (m, 1H), 4.20–3.95 (m, 1H), 3.43–2.15 (1m, 5H), 1.98–1.78 (m, 2H); MS (APCI) m/z 415 $(M-H)^-$.

16-[3-(5-Methoxymethyl)thienyl]-ω-tetranor-3,7-dithiaPGE$_1$ 18-$_{15e}$. 71% yield; IR (neat) 3392, 2921, 1728, 1418, 1263, 1079, 909, 808, 732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.85 (d, $J=3$ Hz, 1H), 6.74 (d, $J=3$ Hz, 1H), 5.9–5.6 (m, 2H), 4.55 (s, 2H), 4.55–4.35 and 4.1–3.9 (m, 2H), 4.3–3.5 (br, 3H), 3.40 (s, 3H), 3.22 (s, 2H), 3.4–3.35 and 3.1–2.3 (m, 10H), 2.0–1.8 (m, 2H); MS (APCI) m/z 459 $(M-H)^-$.

Prostanoid EP and IP receptor binding assay

Membranes from CHO cells expressing the prostanoid receptors were incubated with radioligand (2.5 nM of $[^3H]PGE_2$ 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-receptor 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).

References and Notes

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5. Absolute configuration of 15-OH of the more polar isomers was reconfirmed by their enantioselective synthesis starting from (*R*)-(+)-glycidol. The synthesis will be reported in the following paper.
6. Subtype selectivity of **13-$_{6q}$** ($EC_{50}EP3/EC_{50}EP4$) was reconfirmed by measuring both EP3- and EP4-receptor agonist activities.
7. Kiriyama, M.; Ushikubi, F.; Kobayashi, T.; Hirata, M.; Sugimoto, Y.; Narumiya, S. *Br. J. Pharmacol*. **1997**, *122*, 217.