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Synthesis and Structure–Activity Relationships of a New Class of Selective EP_3 Receptor Agonist, 13,14-Didehydro-16-phenoxy Analogues of Prostaglandin E_1

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Abstract—A series of 13,14-didehydro-16-phenoxy analogues of prostaglandin E_1 was synthesized and their agonistic activity on EP receptor subtypes was evaluated. 13,14-Didehydro-16-phenoxy-1-decarboxy analogues, **7e** and **7f**, display highly selective activity on the EP_3 receptor subtype, thus, their utility as a selective anti-ulcer agent can be expected.

Introduction

Prostaglandins (PGs) play important roles in controlling a multitude of significant physiological processes. Receptors for the prostanoids have been divided into five classes, EP, FP, IP, DP and TP,[1] and recently it has been reported that the EP receptor can be divided into four subtypes, EP_1, EP_2, EP_3 and EP_4, each of which mediates different effects in various tissues and cells.[2] Of these, the EP_3 receptor subtype has been revealed to mediate contraction of the uterus,[3] inhibition of gastric acid secretion,[4] release of neurotransmitters[5] and sodium/water reabsorption in kidney tubules.[6]

Numerous EP_3 receptor agonists have been developed in anticipation of their use as a potent antiulcer drug.[7] However, many of these also demonstrate agonistic activity at the other EP receptor(s), which results in causing side effect(s) such as hypotension and diarrhea, and thus, limiting their clinical use. Therefore, development of a highly selective EP_3-receptor agonist is an attractive research subject.

Among the EP_3-receptor agonists reported so far, PG analogues which have a ω side chain substituted with a phenoxy group at the C-16 (PG-numbering) position such as enprostil[8,9] and GR637999[10] show enhanced agonistic activity at the EP_3 receptor subtype. Some of us have recently revealed that the 13,14-didehydro derivatives of natural PGE have a different spectrum of the biological activities than those of the natural compound.[11] These facts prompted us to investigate biological activities of 13,14-didehydro PGs having a phenoxy-substituted ω side chain, and we report here the synthesis of a series of 13,14-didehydro-16-phenoxy PGE analogues and their biological evaluation with regard to EP receptors (Fig. 1).

Chemistry

13,14-Didehydro-16-phenoxy PGE_1 analogues **5** and their methyl esters **4** were synthesized by using the method developed by us, which includes introduction of the α side chain to *exo*-enone intermediate **1** by an intermolecular radical addition reaction as a more concise reaction than a 1,4-addition reaction using a cuprate (Scheme 1).[12] Thus, *exo*-enone **1**, which was prepared by the reaction of commercial 2-(*N*,*N*-diethylamino)methyl-5-siloxy-2-cyclopentenone[13,14] with the

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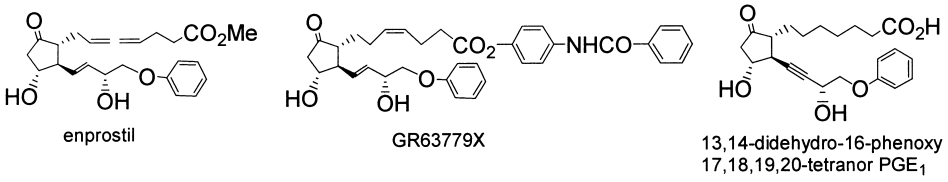
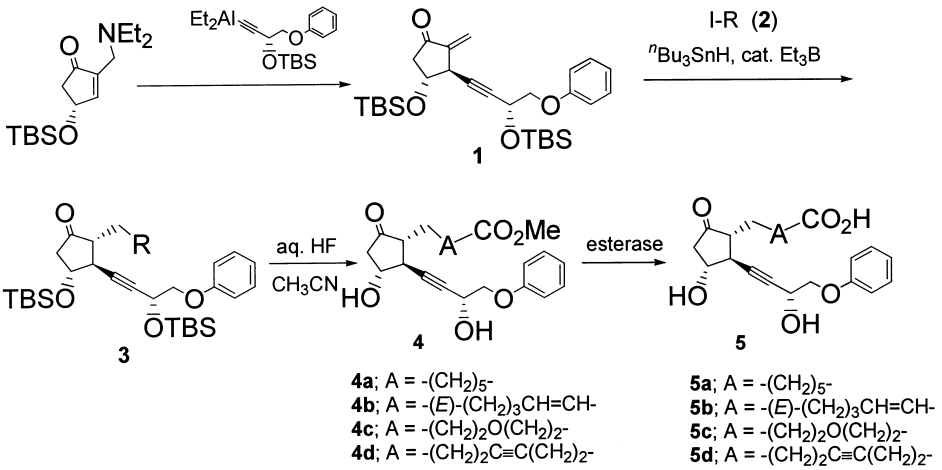


Figure 1.



Scheme 1.

alkynylaluminium reagent corresponding to the ω side chain having a phenoxy group,[15] reacted with the alkyliodide **2** and *n*-Bu_3SnH in the presence of triethylborane at 0 °C to furnish the adduct **3**, which in turn was protodesilylated using aqueous HF in acetonitrile at 0 °C to afford PG methyl esters **4**. The ester moiety in **4** was converted into a carboxylic acid group by hydrolysis using esterase (PLE) to afford PG analogues **5**,[16] because **4** was unstable under the basic condition.

Similarly, PG analogues **6a**–**f** and **7a**–**o** shown in Figure 2 were synthesized from **1** and the corresponding alkyliodides by using the intermolecular radical addition reaction as a key step.

The required α side chain units, alkyliodides **2**, for synthesizing PG analogues **4b**, **5b** and **6** were readily prepared according to the procedure shown in Scheme 2. Thus, (*E*)-6-chloro-2-hexenoic acid, which was prepared from commercial 4-chlorobutanol by Swern oxidation and the following Knoevenagel condensation reaction of the resulting aldehyde with malonic acid, was converted into the esters or amides of (*E*)-6-iodo-2-hexenoic acid by treatment with NaI and the following condensation reaction with alcohol or amine after converting to the corresponding acid chloride. The iodo side chain units **2** for the synthesis of other PGs shown in Scheme 1 and Figure 2 were readily prepared by the conventional methods.

Results and Discussion

The PG analogues prepared here were evaluated for their ability as an agonist on EP_3 receptor by investigating the elastic activities on guinea pig vas deferens[17] and the receptor binding assay. Receptor binding affinities were determined by the displacement of [^{3}H]-PGE_2 from cloned receptors.[18–21] The results, shown in Tables 1–3, are expressed in terms of nano-molar ED_{50}

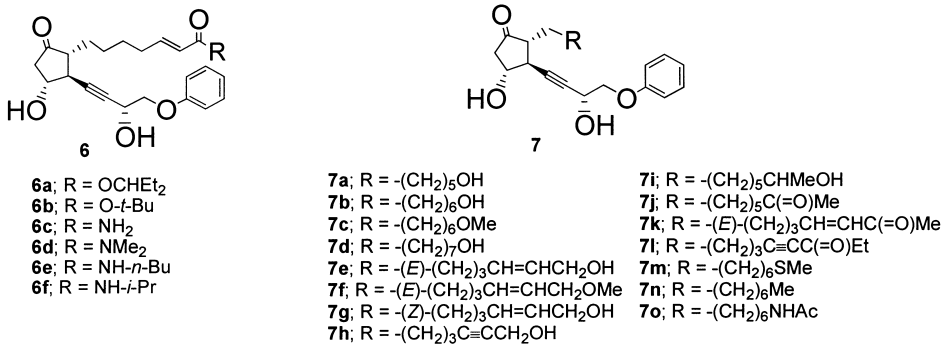
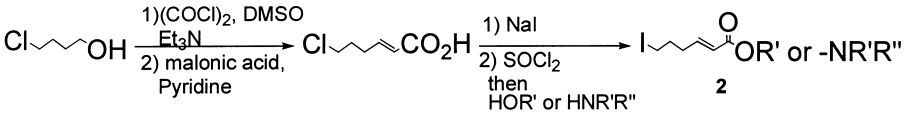


Figure 2.



Scheme 2.

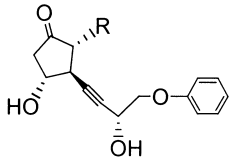
or IC_{50} values, and they show a good relation between in vitro assay on vas deferens and the binding affinity on EP_3.

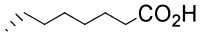
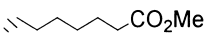
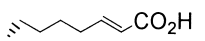
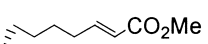
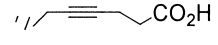
As revealed from Table 1, 13,14-didehydro PGE_1 has a similar spectrum of receptor binding to that of PGE_2, except for the activity on EP_1.[11] Introduction of a phenoxy group into the ω side chain did not enhance the affinity on EP_3 but provided a good selectivity for EP_3. Furthermore, the EP_3 selectivity was considerably improved by converting to the corresponding methyl ester and/or by introducing an unsaturation (double bond) between the C-2 and C-3 positions. Noteworthy is the fact that the methyl ester derivatives exhibited higher activity and selectivity on EP_3 than the corresponding carboxylic acid derivatives as observed on enprostil and its acid derivative.[8,9]

Table 1 indicates that the compound **4b** is a most potent and selective analogue. However, the methyl ester moiety in **4b** may be easily hydrolyzed in vivo to the corresponding acid derivative **5b** and thus it loses its selectivity. Therefore, we next investigated the activities of the compounds **6a**–**f** which have a bulky ester moiety or amide group instead of a methyl ester moiety (Table 2); however, it was found that these modifications reduced the activity on the EP_3 receptor although introduction of a bulky ester group decreased the rate of hydrolysis: the *t*-butyl ester derivative **6b** was hydrolyzed with esterase in plasma at least 3 times more slowly than the compound **4b**.[22]

Based on these results and to design modification suitable to maintain the duration of activity in vivo, we further investigated the ability of 13,14-didehydro-16-phenoxy PGE_1 derivatives having a functional group at the C-1 position other than a carboxyl group (Table 3), and it was found that 1-deoxo analogue of **5a** or **5b**, the compound **7b** or **7e**, respectively, exhibited strong and highly selective activity on the EP_3 receptor. The results shown in Table 3 indicate several features: (1) carbon number (chain length) of the α side chain should be

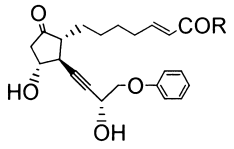
Table 1. EP receptor effects of 13,14-didehydro PGE_1 analogues

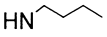


Compound	R	EP_3 (vas deferens) (ED_{50}, nM)	Receptor variants (IC_{50}, nM)[a]			
			EP_3	EP_1	EP_2	EP_4
	PGE_2	N.T.	1.1	0.94	37.7	9.9
	13,14-didehydro PGE_1	N.T.	1.2	>1000	44	9.2
5a		0.07	3.16	97.7	>1000	178
4a		0.08	6.80	>1000	>1000	>1000
5b		0.12	0.26	65.8	>1000	43.3
4b		0.47	0.42	>1000	>1000	>1000
5c		1.44	15.8	N.T.	N.T.	N.T.
4c		10.3	27.0	N.T.	N.T.	N.T.
5d		11.7	58.9	N.T.	N.T.	N.T.
4d		13.7	> 100	N.T.	N.T.	N.T.
	enprostil	0.07	1.72	319	>1000	>1000
	enprostil (Free acid)	0.06	1.87	4.01	>1000	50.8

[a]N.T = not tested.

Table 2. EP receptor effects of 13,14-didehydro PGE_1 analogues



Compound	R	EP_3 (vas deferens) (ED_{50}, nM)	Receptor variants (IC_{50}, nM)[a]			
			EP_3	EP_1	EP_2	EP_4
	PGE_2	0.77	1.14	0.94	37.7	9.92
4b	OMe	0.47	0.42	>1000	>1000	>1000
6a		7.49	36.2	>1000	>1000	>1000
6b		77.6	>100	N.T.	N.T.	N.T.
6c	NH_2	24.5	36.6	141.8	>1000	>1000
6d	NMe_2	55.2	N.T.	N.T.	N.T.	N.T.
6e		63.9	N.T.	N.T.	N.T.	N.T.
6f		101	>100	N.T.	N.T.	N.T.

[a]N.T. = not tested.

adjusted to that of natural PGs (**7b** versus **7a** or **7d**), (2) the olefin geometry of the 2,3-double bond is important (**7e** versus **7g**), (3) introduction of a triple bond into the α side chain cause loss of activity (**7h** and **7l**), (4) oxygen functionality at the C-1 position is necessary or the activity would disappear (**7m**–**o**), and (5) methyl ether derivatives (**7c** and **7f**) and keto compounds (**7j** and **7k**) also exhibited the desired activity.

With these results in hand, we selected the compound **7e** as the most promising candidate to be explored in vivo experiments, and we carried out investigations on inhibition of gastric acid secretion in rat[23] and anti-ulcer activity on the stress ulcer.[24] The results for **7e** are given in Table 4 together with those for **7f**, and it was found that these analogues are effective in both inhibition of acid secretion and protection against the stress ulcer.

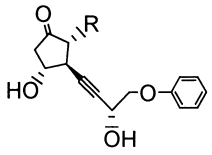
In conclusion, the PGE analogues having a 13,14-didehydro-16-phenoxy structure synthesized here show selective EP_3-receptor agonistic activity. The pharmacological data presented here demonstrate that the compounds **7e** and **7f** with their antisecretory and anti-ulcer activity are potential agents for ulcer therapy.

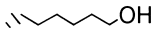
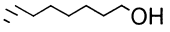
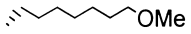
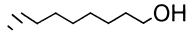
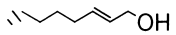
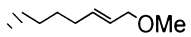
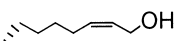
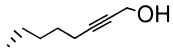
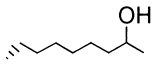
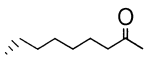
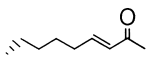
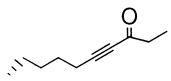
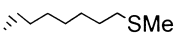
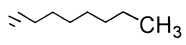
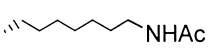
Experimental

Melting points were obtained in open capillary tubes and were uncorrected. The NMR spectra were obtained on either a Varian XL-200 or a Varian XL-300 spectrometer in $CDCl_3$ or DMSO-d_6 with Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin–Elmer 685 spectrometer. Elemental analyses were performed with Perkin–Elmer 2400. TL chromatograms were run on SiG/UV (Wako) using vaniline or $KMnO_4$ as a visualization agent. Mass spectra were recorded with a JMS-SX102 (JEOL) mass spectrometer. All optical rotations were determined at the sodium D line using a DIP-360 (JASCO).

(3*R*,4*R*)-2-methylene-3-[(3*R*)-3-(*t*-butyldimethylsiloxy)-4-phenoxy-1-butynyl]-4-(*t*-butyldimethylsiloxy)cyclopentan-1-on (1). To an ice-cooled solution of (3*R*)-3-(*t*-butyldimethylsiloxy)-4-phenoxy-1-butyne (3.85 g, 13.9 mmol) in toluene (28.8 mL) was added *n*-butyllithium (1.95 M, in hexane solution, 6.4 mL) under an argon atmosphere. After stirring for 30 min, to the mixture was added diethylaluminium chloride (0.97 M in hexane, 14.8 mL), and the resulting mixture was stirred for 30 min at room temperature. After cooling to 0 °C, to this was added (4*R*)-2-(*N*,*N*-diethylamino)methyl-4-(*t*-butyldimethylsiloxy)-cyclopent-2-en-1-on (0.25 M in toluene, 38.4 mL). The resulting mixture was stirred for 15 min at room temperature and poured into a mixture of saturated NH_4Cl aq (100 mL), hexane (100 mL) and 3 N HCl (30 mL). The organic phase was separated and the aqueous phase was extracted with hexane. The combined organic layers were washed with saturated $NaHCO_3$ aq (50 mL), dried over magnesium sulfate, filtered ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/diethyl ether (10/1)) to afford 3.27 g of **1**. oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.15 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 2.33 (dd, J = 18.0, 7.7 Hz, 1H), 2.72 (dd, J = 18.0, 6.5 Hz, 1H), 3.50–3.60 (m, 1H), 3.97–4.09 (m, 2H), 4.23–4.35 (m, 1H), 4.73–4.83 (m, 1H), 5.56 (dd, J = 2.7, 0.6 Hz, 1H), 6.15 (d, J = 3.1 Hz, 1H), 6.85–7.00 (m, 3H), 7.21–7.34 (m, 2H).

Table 3. EP receptor effects of 13,14-didehydro PGE_1 analogues



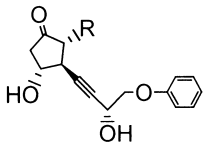
Compound	R	EP_3 (vas deferens) (ED_{50}, nM)	Receptor variants (IC_{50}, nM)[a]			
			EP_3	EP_1	EP_2	EP_4
	PGE_2	0.77	1.14	0.94	37.7	9.92
7a		>100	N.T.	N.T.	N.T.	N.T.
7b		1.55	19.1	>1000	>1000	>1000
7c		>30	N.T.	N.T.	N.T.	N.T.
7d		9.95	N.T.	N.T.	N.T.	N.T.
7e		0.9	5.79	1000	>1000	>1000
7f		10.8	12.6	>1000	>1000	>1000
7g		44.0	70	1000	>1000	>1000
7h		>100	N.T.	N.T.	N.T.	N.T.
7i		>100	N.T.	N.T.	N.T.	N.T.
7j		34.0	7.91	1000	>1000	>1000
7k		38.9	12.46	>1000	>1000	>1000
7l		>100	N.T.	N.T.	N.T.	N.T.
7m		>100	N.T.	N.T.	N.T.	N.T.
7n		>100	N.T.	N.T.	N.T.	N.T.
7o		>100	N.T.	N.T.	N.T.	N.T.

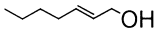
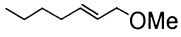
[a]N.T. = not tested.

IR (neat): 2955, 2930, 2886, 2858, 2241, 1737, 1643, 1601, 1589, 1497, 1472, 1389, 1362, 1288, 1251, 1114, 1050, 1007, 975, 838, 780, 754 cm^{-1}.

16-Phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE_1 methyl ester 11,15-bis(*t*-butyldimethylsilyl ether) (3a). To a solution of 6-iodo-2-hexanoate (965 mg, 3.19 mmol) and **1** (800 mg, 1.6 mmol) in toluene (2.0 mL) were added *n*-Bu_3SnH (0.86 mL, 3.19 mmol) and Et_3B (1.0 M in hexane, 0.16 mL) under an argon atmosphere at 0 °C. After stirring for 4 h, the mixture was directly chromatographed on silica gel (hexane/diethyl ether (4/1)) to afford 481 mg of **3a**. oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.13 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 0.91 (s, 9H), 1.17–1.80 (m, 10H), 2.10–2.32 (m, 1H), 2.17 (dd, J = 18.3, 7.4 Hz, 1H), 2.29 (t, J = 7.3 Hz, 2H), 2.60–2.74 (m, 2H), 3.66 (s, 3H), 4.00–4.06 (m, 2H), 4.24–4.35 (m, 1H), 4.72–4.78 (m, 1H), 6.86–6.99 (m, 3H), 7.23–7.32 (m, 2H); IR (neat): 2952, 2931, 2858, 2241, 1747, 1601, 1497, 1464, 1362, 1251, 1172, 1116, 1050, 1007, 976, 838, 780, 755, 692, 670 cm^{-1}; MS (FAB) (+KI) m/z: 669 (MK^+).

Table 4. In vivo-pharmacological activities of 13,14-didehydro PGE_1 analogues



Compound	R	Acidity (T.A.O.[a]) (ED_{30} mg/kg s.c.)	Anti-ulcer (ED_{50}mg/kg p.o)
Famotidine[25]		0.88[b]	0.11
7e		0.013	0.036
7f		0.046	0.053

[a]T.A.O. = total acid output.
[b]ED_{50} mg/kg s.c.

16-Phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE_1 methyl ester (4a). To a solution of **3a** (375 mg, 0.557 mmol) in acetonitrile (18.6 mL) was added 46% HF aq (4.2 mL) at 0 °C. The resulting mixture was stirred for 90 min at 0 °C and poured into a stirred mixture of saturated $NaHCO_3$ aq (97 mL) and AcOEt (150 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt (80 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, concentrated and chromatographed on silica gel (hexane/diethyl ether (1/9)) to afford 211 mg of **4a**. white solid; mp 60–61 °C $[\alpha]_D^{23}$ −32.75 (*c* 0.986, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22–1.83 (m, 10H), 2.22–2.30 (m, 1H), 2.23 (dd, *J* = 18.5, 9.2 Hz, 1H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.63–2.70 (m, 1H), 2.75 (ddd, *J* = 18.5, 7.3, 1.2 Hz, 1H), 2.80 (d, *J* = 3.3 Hz, 1H), 2.97 (d, *J* = 5.0 Hz, 1H), 3.65 (s, 3H), 4.08 (dd, *J* = 9.7, 7.1 Hz, 1H), 4.15 (dd, *J* = 9.7, 3.8 Hz, 1H), 4.30–4.39 (m, 1H), 4.77–4.83 (m, 1H), 6.91–7.02 (m, 3H), 7.27–7.34 (m, 2H); IR (neat): 3430, 2933, 2859, 2241, 1741, 1600, 1588, 1496, 1456, 1374, 1246, 1173, 1081, 1046, 885, 757, 693, 511 cm^{-1}; MS (FAB) *m*/*z*: 403 (MH^+). Anal. calcd for $C_{23}H_{38}O_6$: C, 68.64; H, 7.51. Found: C, 68.45; H, 7.55.

16-Phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE_1 (5a). To a mixture of PLE (sigma, 210 units, suspended in ammonium sulfate, 150 mL) in phosphate buffer (pH = 8, 11 mL) was added a solution of **19a** (91.2 mg) in acetone (1 mL) and the mixture was stirred for 15 h at room temperature. The resulting mixture was acidified (pH = 4) with 0.1 N HCl. After the solution was saturated with ammonium sulfate, the mixture was extracted with AcOEt (20 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/methanol (10/1)) to afford 73.3 mg of **5a**. oil; $[\alpha]_D^{23}$ −16.54 (*c* 0.734, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00–1.84 (m, 10H), 2.16–2.36 (m, 1H), 2.23 (dd, *J* = 18.6, 9.0 Hz, 1H), 2.32 (t, *J* = 7.3 Hz, 2H), 2.65 (ddd, *J* = 11.4, 8.4, 1.9 Hz, 1H), 2.74 (ddd, *J* = 18.6, 7.3, 1.2 Hz, 1H), 4.02–4.17 (m, 2H), 4.28–4.38 (m, 1H), 4.80 (ddd, *J* = 6.9, 3.9, 1.9 Hz, 1H), 6.87–7.02 (m, 3H), 7.24–7.34 (m, 2H); IR (neat): 3402, 2932, 2860, 2238, 1738, 1600, 1588, 1496, 1456, 1385, 1292, 1245, 1173, 1081, 1045, 908, 756, 693, 593, 510 cm^{-1}; MS (FAB) (+KI) *m*/*z*: 427 (MK^+); HRMS *m*/*z*: 395.2043 ($C_{22}H_{29}O_6$, 395.2046).

The following compounds were synthesized from **1** and the corresponding alkyliodide **2** according to the same procedure used for preparation of the compounds **3a**, **4a** and **5a** described above.

(2*E*)-16-Phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE_1 methyl ester (4b). Oil; $[\alpha]_D^{24}$ −24.09 (*c* 0.842, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38–1.86 (m, 6H), 2.13–2.31 (m, 3H), 2.23 (dd, *J* = 18.5, 9.1 Hz, 1H), 2.65 (ddd, *J* = 11.4, 8.3, 1.8 Hz, 1H), 2.76 (ddd, *J* = 18.5, 7.6, 1.3 Hz, 1H), 2.85 (d, *J* = 3.5 Hz, 1H), 3.06 (d, *J* = 5.2 Hz, 1H), 3.71 (s, 3H), 4.08 (dd, *J* = 9.6, 6.9 Hz, 1H), 4.14 (dd, *J* = 9.6, 4.0 Hz, 1H), 4.28–4.40 (m, 1H), 4.75–4.84 (m, 1H), 5.82 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.88–7.04 (m, 4H), 7.24–7.35 (m, 2H); IR (neat): 3412, 2933, 2861, 2241, 1744, 1723, 1656, 1600, 1588, 1496, 1456, 1438, 1385, 1291, 1246, 1174, 1080, 1044, 988, 910, 756, 693 cm^{-1}; MS (FAB) *m*/*z*: 401 (MH^+); HRMS *m*/*z*: 401.1970 ($C_{23}H_{29}O_6$, 401.1964).

(2*E*)-16-Phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE_1 (5b). Oil; $[\alpha]_D^{22}$ −21.40 (*c* 0.995, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) d 1.32–1.85 (m, 6H), 2.17–2.32 (m, 3H), 2.23 (dd, *J* = 18.6, 9.2 Hz, 1H), 2.64 (ddd, *J* = 11.4, 8.3, 1.8 Hz, 1H), 2.75 (ddd, *J* = 18.6, 7.3, 1.3 Hz, 1H), 2.80–4.40 (br, 3H), 4.08 (dd, *J* = 9.6, 6.8Hz, 1H), 4.14 (dd, *J* = 9.6, 3.9 Hz, 1H), 4.29–4.39 (m, 1H), 4.80 (ddd, *J* = 6.8, 3.9, 1.8 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.4 Hz, 1H), 6.90–7.10 (m, 4H), 7.25–7.34 (m, 2H); IR (neat): 3392, 2931, 2861, 2242, 1740, 1696, 1652, 1600, 1588, 1496, 1456, 1417, 1291, 1245, 1173, 1080, 1045, 984, 885, 756, 693 cm^{-1}; MS (FAB) (+KI) *m*/*z*: 425 (MK^+); HRMS *m*/*z*: 387.1810 ($C_{22}H_{27}O_6$, 387.1808).

16-Phenoxy-4-oxa-17,18,19,20-tetranor-13,14-didehydro-PGE_1 methyl ester (4c). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.91 (m, 4H), 2.08–2.49 (m, 3H), 2.24 (dd, *J* = 18.5, 8.9 Hz, 1H), 2.57 (t, *J* = 6.3 Hz, 2H), 2.70 (ddd, *J* = 11.2, 8.0, 1.9 Hz, 1H), 2.75 (ddd, *J* = 18.5, 7.3, 1.3 Hz, 1H), 3.38–3.52 (m, 2H), 3.67 (t, J = 6.3 Hz, 2H), 3.68 (s, 3H), 4.08 (dd, *J* = 9.7, 6.9 Hz, 1H), 4.14 (dd, *J* = 9.7, 4.0 Hz, 1H), 4.27–4.41 (m, 1H), 4.79 (ddd, *J* = 6.9, 4.0, 1.9 Hz, 1H), 6.88–7.05 (m, 3H), 7.24–7.36 (m, 2H); IR (neat): 3412, 2929, 2872, 2239, 1741, 1600, 1588, 1496, 1439, 1365, 1329, 1246, 1175, 1080, 1045, 909, 758, 694, 511 cm^{-1}; MS (SIMS) (+KI) *m*/*z*: 443 (MK^+); HRMS *m*/*z*: 405.1920 ($C_{22}H_{29}O_7$, 405.1913).

16-Phenoxy-4-oxa-17,18,19,20-tetranor-13,14-didehydro-PGE_1 (5c). Oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.56–1.87 (m, 4H), 2.10–2.40 (m, 1H), 2.23 (dd, *J* = 18.5, 9.0 Hz, 1H), 2.57 (t, *J* = 5.9 Hz, 2H), 2.61–2.82 (m, 1H), 2.74 (ddd, *J* = 18.5, 7.3, 1.3 Hz, 1H), 3.38–4.19 (m, 5H), 3.69 (t, *J* = 5.9 Hz, 2H), 4.10 (dd, *J* = 9.7, 6.4 Hz, 1H), 4.15 (dd, *J* = 9.7, 4.4 Hz, 1H), 4.24–4.41 (m, 1H), 4.82 (ddd, *J* = 6.4, 4.4, 1.8 Hz, 1H), 6.82–7.04 (m, 3H),

7.18–7.36 (m, 2H); IR (neat): 3402, 2930, 2873, 2242, 1739, 1600, 1588, 1496, 1456, 1393, 1293, 1246, 1175, 1083, 1046, 909, 758, 694, 594 cm^{-1}; MS (SIMS) (+KI) *m/z*: 429 (MK^+); HRMS *m/z*: 391.1755 ($C_{21}H_{27}O_7$, 391.1757).

16-Phenoxy-17,18,19,20-tetranor-4,4,5,5,13,14-hexadehydro-PGE$_1$ methyl ester (4d). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65–1.82 (m, 1H), 1.90–2.05 (m, 1H), 2.29 (dd, *J* = 18.5, 9.1 Hz, 1H), 2.23–2.54 (m, 6H), 2.71–2.82 (m, 2H), 3.04–3.11 (m, 1H), 3.15–3.21 (m, 1H), 3.29 (s, 2H), 4.09 (dd, *J* = 9.7, 7.0 Hz, 1H), 4.15 (dd, *J* = 9.7, 3.9 Hz, 1H), 4.29–4.41 (m, 1H), 4.76–4.84 (m, 1H), 6.90–7.03 (m, 3H), 7.25–7.34 (m, 2H); IR (neat): 3402, 2930, 2873, 2242, 1739, 1600, 1588, 1496, 1456, 1393, 1293, 1246, 1175, 1083, 1046, 909, 758, 694, 594 cm^{-1}; MS (SIMS) (+KI) *m/z*: 437 (MK^+); HRMS *m/z*: 399.1823 ($C_{23}H_{27}O_6$, 399.1808).

16-Phenoxy-17,18,19,20-tetranor-4,4,5,5,13,14-hexadehydro-PGE$_1$ (5d). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66–1.80 (m, 1H), 1.84–1.98 (m, 1H), 2.29 (dd, *J* = 18.6, 9.1 Hz, 1H), 2.29–2.58 (m, 7H), 2.70–2.86 (m, 2H), 4.11 (dd, *J* = 9.8, 6.7 Hz, 1H), 4.16 (dd, *J* = 9.8, 4.0 Hz, 1H), 4.31–4.44 (m, 1H), 4.35–5.00 (br, 3H), 4.84 (ddd, *J* = 6.6, 4.0, 1.7 Hz, 1H), 6.90–7.04 (m, 3H), 7.25–7.35 (m, 2H); IR (neat): 3401, 2930, 2874, 2244, 1731, 1600, 1496, 1456, 1385, 1290, 1246, 1156, 1077, 1044, 907, 756, 693, 667 cm^{-1}; MS (FAB) (+KI) *m/z*: 423 (MK^+); HRMS *m/z*: 385.1657 ($C_{22}H_{25}O_6$, 385.1651).

(2*E*)-16-Phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE$_1$ 1-ethylpropyl ester (6a). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 7.4 Hz, 6H), 1.38–1.86 (m, 11H), 2.14–2.30 (m, 2H), 2.23 (dd, *J* = 18.5, 9.2 Hz, 1H), 2.64 (ddd, *J* = 11.5, 8.3, 1.9 Hz, 1H), 2.75 (ddd, *J* = 18.5, 7.3, 1.2 Hz, 1H), 3.06–3.34 (br, 2H), 4.08 (dd, *J* = 9.6, 6.9 Hz, 1H), 4.14 (dd, *J* = 9.6, 4.0 Hz, 1H), 4.27–4.39 (m, 1H), 4.73–4.86 (m, 2H), 5.82 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.87–7.03 (m, 4H), 7.25–7.35 (m, 2H); IR (neat): 3418, 2970, 2937, 2879, 2242, 1745, 1714, 1653, 1600, 1588, 1497, 1460, 1384, 1246, 1174, 1104, 1081, 1046, 990, 910, 756, 693, 595, 510 cm^{-1}; MS (LSIMS) (+KI) *m/z*: 457 (MK^+); HRMS *m/z*: 457.2597 ($C_{27}H_{36}O_6K$, 457.2590).

(2*E*)-16-Phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE$_1$ *t*-butyl ester (6b). Oil; $[\alpha]_D^{23}$ −18.80 (*c* 1.64, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40–1.86 (m, 6H), 1.48 (s, 9H), 2.11–2.31 (m, 3H), 2.23 (dd, *J* = 18.6, 9.2 Hz, 1H), 2.65 (ddd, *J* = 11.3, 8.2, 1.8 Hz, 1H), 2.76 (ddd, *J* = 18.6, 7.3, 1.3 Hz, 1H), 4.09 (dd, *J* = 9.6, 6.8 Hz, 1H), 4.14 (dd, *J* = 9.6, 4.1 Hz, 1H), 4.28–4.39 (m, 1H), 4.76–4.83 (m, 1H), 5.74 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.84 (dt, *J* = 15.6, 7.0 Hz, 1H), 6.90–7.03 (m, 3H), 7.24–7.35 (m, 2H); IR (neat): 3413, 2978, 2933, 2862, 2242, 1746, 1713, 1651, 1600, 1589, 1497, 1456, 1393, 1369, 1318, 1246, 1158, 1081, 1046, 986, 851, 756, 693 cm^{-1}; MS (FAB) (+KI) *m/z*: 481 (MK^+); HRMS *m/z*: 443.2430 ($C_{26}H_{35}O_6$, 443.2433).

(2*E*)-16-Phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE$_1$ amide (6c). Oil; $[\alpha]_D^{24}$ −38.49 (*c* 0.53, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26–1.71 (m, 6H), 2.00–2.24 (m, 3H), 2.06 (dd, *J* = 18.2, 7.9 Hz, 1H), 2.52–2.65 (m, 2H), 3.96 (dd, *J* = 9.8, 6.6 Hz, 1H), 3.99 (dd, *J* = 9.8, 5.0 Hz, 1H), 4.09–4.21 (m, 1H), 4.54–4.63 (m, 1H), 5.46 (d, *J* = 5.5 Hz, 1H), 5.69 (d, *J* = 6.0 Hz, 1H), 5.84 (d, *J* = 15.5 Hz, 1H), 6.58 (dt, *J* = 15.5, 6.9 Hz, 1H), 6.87 (brs, 1H), 6.90–6.97 (m, 3H), 7.24–7.35 (m, 3H); IR (neat): 3493, 3458, 3359, 3208, 2938, 2915, 2859, 2234, 1721, 1673, 1640, 1609, 1587, 1492, 1455, 1439, 1402, 1326, 1294, 1276, 1249, 1173, 1150, 1103, 1066, 1046, 901, 877, 765, 697, 665 cm^{-1}; MS (LSIMS) *m/z*: 386 (MH^+). Anal. calcd for $C_{22}H_{27}N_1O_5$: C, 68.55; H, 7.06 N, 3.63. Found: C, 68.49; H, 6.95; N, 3.57.

(2*E*)-16-Phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE$_1$ *N*,*N*-dimethylamide (6d). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37–1.96 (m, 6H), 2.12–2.35 (m, 3H), 2.23 (dd, *J* = 18.5, 9.1 Hz, 1H), 2.51 (brs, 2H), 2.65 (ddd, *J* = 11.3, 8.2, 1.7 Hz, 1H), 2.74 (ddd, *J* = 18.5, 7.3, 1.2 Hz, 1H), 3.02 (s, 6H), 4.10 (dd, *J* = 9.8, 6.5 Hz, 1H), 4.13 (dd, *J* = 9.8, 4.8 Hz, 1H), 4.25–4.37 (m, 1H), 4.80 (ddd, *J* = 6.5, 4.8, 1.7 Hz, 1H), 6.23 (d, *J* = 15.0 Hz, 1H), 6.84–7.03 (m, 3H), 6.90 (dt, *J* = 15.0, 7.5 Hz, 1H), 7.24–7.36 (m, 2H); IR (neat): 3368, 3012, 2933, 2861, 2240, 1744, 1659, 1601, 1496, 1456, 1401, 1292, 1247, 1156, 1081, 1046, 982, 885, 756, 693, 666, 511 cm^{-1}; MS (LSIMS) (+KI) *m/z*: 452 (MK^+); HRMS *m/z*: 414.2287 ($C_{24}H_{32}N_1O_5$, 414.2281).

(2*E*)-16-Phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE$_1$ *N*-*n*-butylamide (6e). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.27–1.89 (m, 10H), 2.12–2.30 (m, 3H), 2.23 (dd, *J* = 18.6, 9.0 Hz, 1H), 2.65 (ddd, *J* = 11.3, 8.3, 1.8 Hz, 1H), 2.67–2.99 (br, 2H), 2.74 (ddd, *J* = 18.6, 7.3, 1.2 Hz, 1H), 3.24–3.34 (m, 2H), 4.09 (dd, *J* = 9.6, 6.5 Hz, 1H), 4.15 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.26–4.37 (m, 1H), 4.80 (ddd, *J* = 6.5, 4.8, 1.8 Hz, 1H), 5.70 (brt, 1H), 5.77 (d, *J* = 15.3 Hz, 1H), 6.81 (dt, *J* = 15.3, 7.3 Hz, 1H), 6.91–7.02 (m, 3H), 7.26–7.34 (m, 2H); IR (neat): 3328, 2933, 2863, 2240, 1741, 1669, 1628, 1601, 1549, 1497, 1457, 1374, 1246, 1155, 1081, 1047, 983, 756, 693 cm^{-1}; MS (FAB) (+KI) *m/z*: 480 (MK^+); HRMS *m/z*: 442.2580 ($C_{26}H_{36}N_1O_5$, 442.2594).

(2*E*)-16-Phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE$_1$ *N*-isopropylamide (6f). Oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (d, *J* = 6.5 Hz, 6H), 1.31–1.92 (m, 6H), 2.08–2.36 (m, 3H), 2.22 (dd, *J* = 18.5, 9.0 Hz, 1H), 2.65 (ddd, *J* = 11.2, 8.3, 1.9 Hz, 1H), 2.74 (ddd, *J* = 18.5, 7.2, 1.1 Hz, 1H), 3.96–4.39 (m, 4H), 4.74–4.84 (m, 1H), 5.46 (d, *J* = 7.9 Hz, 1H), 5.72 (d, *J* = 15.2 Hz, 1H), 6.79 (dt, *J* = 15.2, 7.0 Hz, 1H), 6.89–7.03 (m, 3H), 7.23–7.36 (m, 2H); IR (neat): 3306, 2974, 2932, 2861, 2242, 1742, 1667, 1623, 1601, 1548, 1497, 1457, 1367, 1335, 1291, 1246, 1172, 1081, 1046, 983, 884, 756, 693, 667 cm^{-1}; MS (FAB) (+KI) *m/z*: 466 (MK^+); HRMS *m/z*: 428.2442 ($C_{25}H_{34}N_1O_6$, 428.2437).

2-Decarboxy-2-hydroxy-16-phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE$_1$ (7a). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20–1.91 (m, 10H), 2.20–2.31 (m, 1H), 2.23

(dd, $J=18.5$, 9.3 Hz, 1H), 2.64 (ddd, $J=11.5$, 8.4, 1.9 Hz, 1H), 2.74 (ddd, $J=18.5$, 7.3, 1.3 Hz, 1H), 3.32–3.55 (br, 2H), 3.61 (t, $J=6.5$ Hz, 2H), 4.07 (dd, $J=9.6$, 7.0 Hz, 1H), 4.13 (dd, $J=9.6$, 3.9 Hz, 1H), 4.25–4.38 (m, 1H), 4.75–4.85 (m, 1H), 6.88–7.05 (m, 3H), 7.25–7.35 (m, 2H); IR (neat): 3369, 2932, 2859, 2242, 1740, 1600, 1588, 1496, 1456, 1403, 1385, 1293, 1246, 1156, 1080, 1047, 909, 757, 693, 510 cm^{-1}; MS (FAB) (+KI) m/z: 399 (MK^+); HRMS m/z: 361.2029 ($C_{21}H_{29}O_5$, 361.2015).

2-Decarboxy-2-hydroxymethyl-16-phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE$_1$ (7b). Oil; $[\alpha]_D^{23}$ −24.10 (*c* 1.17, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00–1.94 (m, 12H), 2.05–2.35 (m, 1H), 2.23 (dd, $J=18.6$, 9.3 Hz, 1H), 2.65 (ddd, $J=11.4$, 8.3, 1.7 Hz, 1H), 2.74 (ddd, $J=18.6$, 7.3, 1.2 Hz, 1H), 3.20–3.68 (br, 2H), 3.62 (t, $J=6.4$ Hz, 2H), 4.07 (dd, $J=9.6$, 7.1 Hz, 1H), 4.13 (dd, $J=9.6$, 3.6 Hz, 1H), 4.27–4.38 (m, 1H), 4.78 (ddd, $J=6.8$, 3.8, 1.8 Hz, 1H), 6.87–7.06 (m, 3H), 7.25–7.36 (m, 2H); IR (neat): 3392, 2931, 2858, 2242, 1742, 1600, 1588, 1496, 1456, 1374, 1292, 1246, 1172, 1080, 1047, 910, 756, 693, 594, 510 cm^{-1}; MS (LSIMS) (+KI): 413 (MK^+); HRMS m/z: 375.2042 ($C_{22}H_{31}O_5$, 375.2034).

2-Decarboxy-2-methoxymethyl-16-phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE$_1$ (7c). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18–1.88 (m, 12H), 2.20–2.31 (m, 1H), 2.23 (dd, $J=18.5$, 9.3 Hz, 1H), 2.65 (ddd, $J=11.4$, 8.3, 1.8 Hz, 1H), 2.74 (ddd, $J=18.5$, 7.3, 1.3 Hz, 1H), 3.15–3.42 (m, 2H), 3.32 (s, 3H), 3.35 (t, $J=6.6$ Hz, 2H), 4.07 (dd, $J=9.7$, 7.1 Hz, 1H), 4.13 (dd, $J=9.7$, 4.1 Hz, 1H), 4.27–4.39 (m, 1H), 4.74–4.85 (m, 1H), 6.90–7.05 (m, 3H), 7.25–7.36 (m, 2H); IR (neat): 3402, 2931, 2858, 2242, 1746, 1600, 1588, 1497, 1456, 1374, 1292, 1246, 1156, 1083, 1046, 910, 756, 693, 594, 510 cm^{-1}; MS (FAB) (+KI): 427 (MK^+); HRMS m/z: 389.2344 ($C_{23}H_{33}O_5$, 389.2328).

2-Decarboxy-2-hydroxyethyl-16-phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE$_1$ (7d). White solid; mp 84–85 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19–1.85 (m, 14H), 2.20–2.34 (m, 1H), 2.23 (dd, $J=18.5$, 9.4 Hz, 1H), 2.65 (ddd, $J=11.5$, 8.3, 1.8 Hz, 1H), 2.74 (ddd, $J=18.5$, 7.3, 1.3 Hz, 1H), 3.20–3.34 (br, 1H), 3.35–3.48 (br, 1H), 3.62 (t, $J=6.6$ Hz, 2H), 4.07 (dd, $J=9.7$, 7.1 Hz, 1H), 4.13 (dd, $J=9.7$, 4.0 Hz, 1H), 4.26–4.38 (m, 1H), 4.74–4.83 (m, 1H), 6.85–7.03 (m, 3H), 7.25–7.36 (m, 2H); IR (neat): 3403, 2920, 2855, 2238, 1740, 1601, 1589, 1499, 1467, 1455, 1412, 1366, 1331, 1301, 1280, 1241, 1196, 1173, 1153, 1116, 1093, 1074, 1051, 1004, 908, 882, 754, 691, 602, 577, 534, 506 cm^{-1}; MS (FAB) (+KI) m/z: 427 (MK). Anal. calcd for $C_{23}H_{30}O_5$: C, 71.11; H, 8.30. Found: C, 70.96; H, 8.40.

(2*E*)-2-Decarboxy-2-hydroxymethyl-16-phenoxy-17,18,19,20-tetranor-2,3,13,14-tetra-dehydro-PGE$_1$ (7e). $[\alpha]_D^{23}$ −21.96 ($c=1.02$, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30–1.85 (m, 6H), 1.94–2.12 (m, 2H), 2.16–2.34 (m, 1H), 2.23 (dd, $J=18.6$, 9.1 Hz, 1H), 2.34–2.60 (br, 3H), 2.66 (ddd, $J=11.5$, 8.2, 1.8 Hz, 1H), 2.74 (ddd, $J=18.6$, 7.3, 1.4 Hz, 1H), 4.03–4.17 (m, 4H), 4.28–4.38 (m, 1H), 4.78 (ddd, $J=6.9$, 4.0, 1.8 Hz, 1H), 5.56–5.72 (m, 2H), 6.90–7.04 (m, 3H), 7.25–7.35 (m, 2H); IR (neat): 3369, 3013, 2931, 2860, 2242, 1742, 1600, 1588, 1496, 1456, 1385, 1292, 1155, 1082, 1046, 973, 909, 755, 692, 667, 594, 510 cm^{-1}; MS (FAB) (+KI) m/z: 429 (MK^+); HRMS m/z: 373.2025 ($C_{22}H_{29}O_5$, 373.2015).

(2*E*)-2-Decarboxy-2-methoxymethyl-16-phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE$_1$ (7f). Oil; $[\alpha]_D^{22}$ −27.86 (*c* 0.974, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30–1.84 (m, 6H), 1.98–2.10 (m, 2H), 2.17–2.30 (m, 1H), 2.23 (dd, $J=18.6$, 9.0 Hz, 1H), 2.65 (ddd, $J=11.2$, 8.1, 1.8 Hz, 1H), 2.74 (ddd, $J=18.6$, 7.3, 1.4 Hz, 1H), 2.70–3.06 (br, 2H), 3.31 (s, 3H), 3.85 (dd, $J=6.0$, 0.9 Hz, 2H), 4.07 (dd, $J=9.6$, 7.1 Hz, 1H), 4.13 (dd, $J=9.6$, 4.0 Hz, 1H), 4.28–4.38 (m, 1H), 4.78 (ddd, $J=7.1$, 4.0, 1.9 Hz, 1H), 5.48–5.73 (m, 2H), 6.90–7.03 (m, 3H), 7.26–7.35 (m, 2H); IR (neat): 3401, 2930, 2859, 2241, 1744, 1600, 1588, 1496, 1454, 1385, 1292, 1246, 1154, 1078, 1046, 975, 908, 756, 693, 595, 509 cm^{-1}; MS (FAB) (+KI) m/z: 425 (MK^+); HRMS m/z: 387.2176 ($C_{23}H_{31}O_5$, 387.2172).

(2*Z*)-2-Decarboxy-2-hydroxymethyl-16-phenoxy-17,18,19,20-tetranor-2,3,13,14-tetranor-PGE$_1$ (7g). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25–2.16 (m, 9H), 2.20–2.29 (m, 1H), 2.23 (dd, $J=18.5$, 9.1 Hz, 1H), 2.66 (ddd, $J=11.3$, 8.2, 1.8 Hz, 1H), 2.74 (ddd, $J=18.5$, 7.3, 1.3 Hz, 1H), 3.20–3.38 (br, 1H), 3.39–3.62 (br, 1H), 4.07 (dd, $J=9.6$, 6.9 Hz, 1H), 4.13 (dd, $J=9.6$, 4.1 Hz, 1H), 4.18 (d, $J=6.6$ Hz, 2H), 4.26–4.38 (m, 1H), 4.69–4.85 (m, 1H), 5.42–5.67 (m, 2H), 6.89–7.03 (m, 3H), 7.25–7.35 (m, 2H); IR (neat): 3369, 3014, 2931, 2860, 2242, 1741, 1600, 1588, 1496, 1456, 1385, 1293, 1246, 1155, 1081, 1045, 912, 756, 693, 503 cm^{-1}; MS (FAB) (+KI) m/z: 411 (MK^+); HRMS m/z: 411.1578 ($C_{22}H_{28}O_5K$, 411.1574).

2-Decarboxy-2-hydroxymethyl-16-phenoxy-17,18,19,20-tetranor-2,2,3, 3, 13,14-hexadehydro-PGE$_1$ (7h). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42–1.90 (m, 6H), 2.17–2.33 (m, 4H), 2.25 (dd, $J=18.6$, 9.2 Hz, 1H), 2.70 (ddd, $J=11.4$, 8.3, 1.8 Hz, 1H), 2.76 (ddd, $J=18.6$, 7.3, 1.3 Hz, 1H), 3.17 (d, $J=3.6$ Hz, 1H), 3.27 (d, $J=5.2$ Hz, 1H), 4.10 (dd, $J=9.7$, 6.9 Hz, 1H), 4.15 (dd, $J=9.7$, 4.1 Hz, 1H), 4.20–4.27 (m, 2H), 4.29–4.40 (m, 1H), 4.76–4.84 (m, 1H), 6.91–7.04 (m, 3H), 7.26–7.35 (m, 2H); IR (neat): 3392, 2936, 2864, 2286, 2233, 1741, 1600, 1588, 1496, 1456, 1375, 1293, 1246, 1153, 1080, 1045, 1016, 911, 757, 693, 595 cm^{-1}; MS (LSIMS) (+KI): 409 (MK^+); HRMS m/z: 409.1429 ($C_{22}H_{26}O_5K$, 409.1418).

2-Decarboxy-2-(1′-hydroxyethyl)-16-phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE$_1$ (7i). Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20–1.87 (m, 12H), 1.17 (d, $J=6.2$ Hz, 3H), 2.20–2.35 (m, 1H), 2.23 (dd, $J=18.5$, 9.3 Hz, 1H), 2.65 (ddd, $J=11.4$, 8.4, 2.0 Hz, 1H), 2.74 (ddd, $J=18.5$, 7.3, 1.3 Hz, 1H), 3.25–3.44 (br, 2H), 3.71–3.84 (m, 1H), 4.07 (dd, $J=9.7$, 7.1 Hz, 1H), 4.13 (dd, $J=9.7$, 4.0 Hz, 1H), 4.26–4.39 (m, 1H), 4.75–4.82 (m, 1H), 6.87–7.03 (m, 3H), 7.25–7.35 (m, 2H); IR (neat): 3392, 2931, 2858, 2242, 1741, 1600, 1589, 1496, 1456, 1375, 1292, 1246, 1156, 1082, 1047, 909, 756, 692,

667, 510 cm^{-1}; MS (FAB) (+KI) *m/z*: 427 (MK^+); HRMS *m/z*: 389.2015 ($C_{23}H_{33}O_5$, 389.2022).

2-Decarboxy-2-acetyl-16-phenoxy-17,18,19,20-tetranor-13,14-didehdro-PGE$_1$ (7j). White solid; mp 66.5–67.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18–1.85 (m, 10H), 2.11 (s, 3H), 2.21–2.30 (m, 1H), 2.24 (dd, *J* = 18.5, 9.2 Hz, 1H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.65 (ddd, *J* = 11.4, 8.4, 1.8 Hz, 1H), 2.74 (ddd, *J* = 18.5, 7.3, 1.3 Hz, 1H), 3.31 (d, *J* = 4.2 Hz, 2H), 4.08 (dd, *J* = 9.7, 7.0 Hz, 1H), 4.13 (dd, *J* = 9.7, 4.0 Hz, 1H), 4.26–4.40 (m, 1H), 4.75–4.85 (m, 1H), 4.75–4.85 (m, 1H), 6.88–7.04 (m, 3H), 7.25–7.35 (m, 2H); IR (neat): 3367, 3270, 2930, 2858, 2233, 1751, 1708, 1601, 1588, 1499, 1456, 1413, 1371, 1339, 1302, 1294, 1242, 1215, 1201, 1174, 1149, 1104, 1085, 1045, 902, 878, 816, 749, 689, 596, 507 cm^{-1}; MS (FAB) (+KI) *m/z*: 425 (MK^+). Anal. calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.42; H, 7.92.

(2*E*)-2-Decarboxy-2-acetyl-16-phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydro-PGE$_1$ (7k). Oil; $[\alpha]_D^{22}$ −24.99 (*c* = 1.33, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.84 (m, 6H), 2.16–2.30 (m, 3H), 2.23 (dd, *J* = 18.6, 9.1 Hz, 1H), 2.24 (s, 3H), 2.65–3.00 (br, 2H), 2.64 (ddd, *J* = 11.4, 8.2, 1.8 Hz, 1H), 2.75 (ddd, *J* = 18.6, 7.3, 1.3 Hz, 1H), 4.08 (dd, *J* = 9.7, 6.8 Hz, 1H), 4.13 (dd, *J* = 9.7, 4.0 Hz, 1H), 4.29–4.39 (m, 1H), 4.79 (ddd, J = 6.8, 4.0, 1.8 Hz, 1H), 6.07 (dt, *J* = 16.0, 1.4 Hz, 1H), 6.77 (dt, *J* = 16.0, 6.9 Hz, 1H), 6.90–7.04 (m, 3H), 7.25–7.35 (m, 2H); IR (neat): 3401, 2932, 2861, 2242, 1744, 1670, 1625, 1600, 1588, 1496, 1456, 1427, 1364, 1292, 1247, 1155, 1081, 1045, 982, 910, 757, 694, 593 cm^{-1}; MS (FAB) (+KI) *m/z*: 423 (MK^+); HRMS *m/z*: 385.2026 ($C_{23}H_{29}O_5$, 385.2015).

2-Decarboxy-2-propionyl-16-phenoxy-17,18,19,20-tetranor-2,2,3,3,13,14-hexadehydro-PGE$_1$ (7l). Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, *J* = 7.4 Hz, 3H), 1.45–1.87 (m, 6H), 2.210–2.40 (m, 3H), 2.24 (dd, *J* = 18.6, 9.1 Hz, 1H), 2.55 (q, *J* = 7.4 Hz, 2H), 2.66 (ddd, *J* = 11.2, 8.2, 1.8 Hz, 1H), 2.75 (ddd, *J* = 18.6, 7.2, 1.2 Hz, 1H), 3.17–3.30 (m, 2H), 4.08 (dd, *J* = 9.5, 6.9 Hz, 1H), 4.14 (dd, *J* = 9.5, 4.2 Hz, 1H), 4.28–4.43 (m, 1H), 4.74–4.86 (m, 1H), 6.90–7.04 (m, 3H), 7.25–7.36 (m, 2H); IR (neat): 3419, 2938, 2866, 2211, 1744, 1672, 1600, 1588, 1496, 1458, 1409, 1376, 1293, 1246, 1176, 1079, 1046, 913, 799, 757, 693, 593, 511 cm^{-1}; MS (FAB) (+KI): 435 (MK^+); HRMS *m/z*: 397.2006 ($C_{24}H_{29}O_5$, 397.2015).

2-Decarboxy-2-methylthiomethyl-16-phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE$_1$ (7m). White solid; mp 75.5–76.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21–1.84 (m, 12H), 2.08 (s, 3H), 2.20–2.31 (m, 1H), 2.23 (dd, *J* = 18.5, 9.3 Hz, 1H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.65 (ddd, *J* = 11.5, 8.4, 1.9 Hz, 1H), 2.75 (ddd, *J* = 18.5, 7.3, 1.3 Hz, 1H), 3.19 (d, *J* = 4.9 Hz, 1H), 3.41 (d, *J* = 3.3 Hz, 1H), 4.07 (dd, *J* = 9.7, 7.2 Hz, 1H), 4.13 (dd, *J* = 9.7, 3.8 Hz, 1H), 4.28–4.40 (m, 1H), 4.76–4.85 (m, 1H), 6.89–7.03 (m, 3H), 7.25–7.35 (m, 2H); IR (neat): 3370, 2926, 2850, 2240, 1748, 1601, 1589, 1499, 1468, 1456, 1370, 1340, 1302, 1292, 1238, 1197, 1175, 1147, 1081, 1048, 909, 881, 812, 748, 689, 545, 507 cm^{-1}; MS (FAB) (+KI) *m/z*: 443 (MK^+). Anal. calcd for $C_{23}H_{32}O_4S$:C, 68.28; H, 7.97. Found: C, 68.00; H, 8.02.

2-Decarboxy-2-ethyl-16-phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE$_1$ (7n). White solid; mp 51.5–53.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, *J* = 6.6 Hz, 3H), 1.16–1.85 (m, 14H), 2.22–2.34 (m, 1H), 2.23 (dd, *J* = 18.5, 9.5 Hz, 1H), 2.66 (ddd, *J* = 11.4, 8.4, 1.8 Hz, 1H), 2.74 (ddd, *J* = 18.5, 7.3, 1.4 Hz, 1H), 2.96 (d, *J* = 4.7 Hz, 1H), 3.16 (d, *J* = 3.0 Hz, 1H), 4.07 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.14 (dd, *J* = 9.6, 3.7 Hz, 1H), 4.27–4.41 (m, 1H), 4.75–4.84 (m, 1H), 6.86–7.04 (m, 3H), 7.25–7.36 (m, 2H); IR (neat): 3369, 2921, 2850, 2239, 1752, 1729, 1602, 1589, 1500, 1468, 1456, 1371, 1341, 1292, 1244, 1175, 1147, 1127, 1085, 1048, 904, 880, 814, 750, 726, 691, 508 cm^{-1}; MS (FAB) (+KI) *m/z*: 411 (MK^+). Anal. calcd for $C_{23}H_{32}O_4$:C, 74.16; H, 8.66. Found: C, 73.88; H, 8.60.

2-Decarboxy-2-acetamidomthyl-16-phenoxy-17,18,19,20-tetranor-13,14-didehydro-PGE$_1$ (7o). Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20–1.85 (m, 12H), 1.98 (s, 3H), 2.17–2.36 (m, 1H), 2.24 (dd, *J* = 18.5, 9.1 Hz, 1H), 2.68 (ddd, *J* = 11.3, 8.2, 1.8 Hz, 1H), 2.74 (ddd, *J* = 18.5, 7.3, 1.3 Hz, 1H), 2.85–3.35 (m, 4H), 4.08 (dd, *J* = 9.7, 6.9 Hz, 1H), 4.13 (dd, *J* = 9.7, 4.4 Hz, 1H), 4.28–4.39 (m, 1H), 4.79 (ddd, *J* = 6.9, 4.4, 1.8 Hz, 1H), 5.67–5.81 (br, 1H), 6.88–7.02 (m, 3H), 7.24–7.34 (m, 2H); IR (neat): 3307, 2930, 2857, 2240, 1742, 1651, 1600, 1588, 1559, 1496, 1456, 1371, 1293, 1246, 1155, 1081, 1045, 909, 756, 693, 598, 509 cm^{-1}; MS (FAB) (+KI) *m/z*: 454 (MK^+); HRMS *m/z*: 416.2455 ($C_{24}H_{34}N_1O_5$, 416.2437).

Determination of EP$_3$ activity (vas deferens)

Male guinea-pigs were killed by a blow to the head followed by exsanguination. Preparations of vas deferens were mounted in organ baths for recording of tension with isometric transducers. The bathing solution was aerated with 95% O_2 and 5% CO_2 and maintained at 37 °C. Lengths (20 mm) of vas deferens were suspended in Krebs solution (no additions) between electrodes for supra-maximal electrical field stimulation (supramaximal voltage 1 ms, 10 Hz for 1 s every 32 s). 13,14-Didehydro PGE_1 derivative doses were added cumulatively. Log concentration-inhibition curves were constructed.

EP$_1$∼EP$_4$ receptor binding assay

[5,6,8,11,12,14,15-^{3}H]PGE_2 (200 Ci/mmol) was obtained from Daiichikagaku, [^{3}H] iloprost (14.1 Ci/mmol), and iloprost were obtained from Amersham Corp. PGE_2 was purchased from Funakoshi Phamaceuticals (Tokyo, Japan). All other chemicals were of reagent grade. The establishment of Chinese hamster ovary (CHO) cell line stable expressing each prostanoid receptor has been described previously.

The harvested CHO cells expressing each receptor subtype were homogenized using a Potter-Elvehjem homogenizer in 10 mM Tris–HCl (pH 7.4), containing 10 mM $MgCl_2$, 1 mM EDTA, 20 mM indomethacin, and 0.1 mM phenylmethylsulfonyl fluoride. The membrane

fraction (250,000×*g* pellet) was washed and suspended in the same buffer. The standard mixture comprised 4 nM [^{3}H] PGE_2 and 80 μg of the membrane prepared from each receptor-expressing CHO cell type in 100 μl of 10 mM Mes-NaOH, pH 6.0, containing 10 mM $MgCl_2$ and 1 mM EDTA (buffer A). After incubation at 30 °C for 1 h (10 min for EP_1 receptor), the reaction was terminated by the addition of ice-cold buffer A, after which the mixture was rapidly filtered through a Whatman GF/C filter. The filter was then washed with ice-cold buffer A and the radioactivity associated with the filter was measured by a liquid scintillation counter. Nonspecific binding was determined using a 1000-fold excess of the respective unlabeled PGs in the incubation mixture. The specific binding was calculated by subtracting the non-specific binding from the total binding.

Gastric acid secretion studies in pylorus-ligated rat

Male Wistar strain rats (SLC, Shizuoka, Japan) were used. They were kept in stainless steel cages and fasted but were allowed free access to water for 18 h before the experiments. The fasted animals were anesthetized with ether and pylorus ligated following abdominal midline incision. The animals were treated with 13,14-didehydro PGE1 derivatives for 30 min before the operation. After 4 h the animals were sacrificed for collection of gastric juice. The volume and acidity of the gastric juice were determined. The acidity of gastric juice was measured by titration with 0.1 N NaOH up to pH 7.0 with phenolphthalein as the indicator. Total acid output (TAO) was calculated from the product of the acidity and the volume of the gastric juice.

Gastric ulcer studies

The animals were fasted for 18 h. RWIS ulcer was induced according to the general method. Rats were placed in a stainless steel stress cage and immersed vertically to the level of the xiphoid process in a water bath maintained at 23 °C. After the immersion for 7 h the animals were sacrificed under anesthesia with ether.

The stomachs were removed and inflated with 10 mL of 1% formaline solution and were placed in the same solution for 15 min. They were then opened along the greater curvatures. The area of each ulcer in the corpus and antrum portion was measured under stereoscopic microscopy, and 13,14-didehydro PGE_1 derivatives were administered 10 min before the immersion.

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