Rational Design of Antitumor Prostaglandins with High Biological Stability

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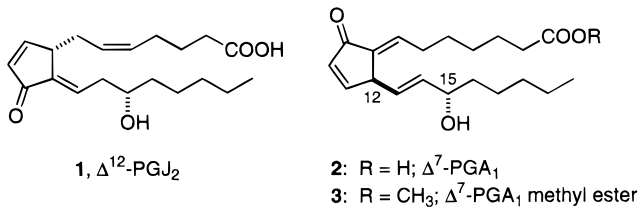
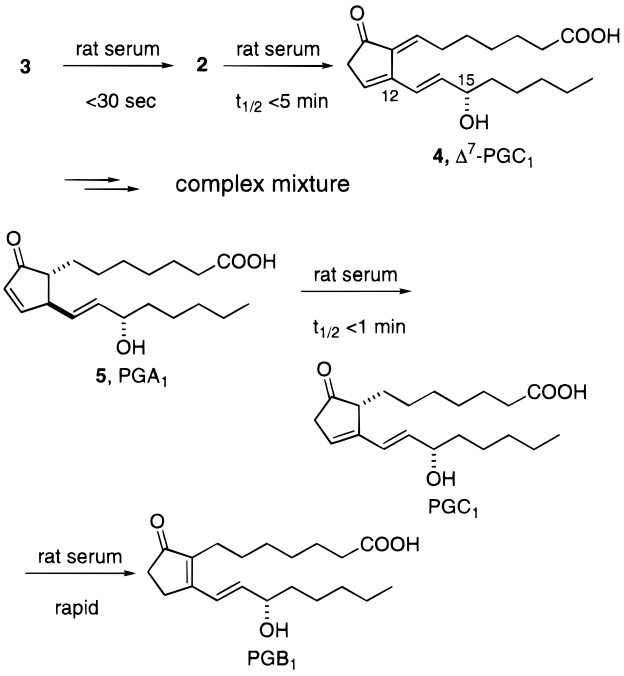
Molecular design can overcome the metabolic instability of Δ^7-PGA$_1$, while maintaining its antitumor potency. Saturation of the C(13)−C(14) double bond enhances the biological stability but decreases the antiproliferative activity. Configurational inversion of the isomerase-sensitive C(12) stereocenter from the natural *S* to the unnatural *R* geometry not only enhances biological stability but also significantly suppresses the growth of the tumor cells. The 12*R* derivatives markedly increase the induction of p21, a Cdk inhibitor, leading to sharp cell cycle arrest at the G$_1$ phase at a dose level so low that at this dose Δ^7-PGA$_1$ methyl ester scarcely exerts an effect. These conspicuous biological properties lead to long-term suppression of tumor cell growth. The structure−stability relationship demonstrates that the stability of prostaglandins (PGs) is crucially controlled by the C(12) configuration and is unaffected by the geometry of the hydroxy-bearing C(15). The successful design of antitumor PGs resistant to enzymatic metabolism provides a new strategy applicable to creating a useful PG for cancer chemotherapy.

Introduction

Much attention has been devoted to antineoplastic and antiviral prostaglandins (PGs),[1] particularly the cross-conjugated dienone PGs such as Δ^{12}-PGJ$_2$ (**1**), Δ^7-PGA$_1$ (**2**), and its methyl ester (**3**).[2] They exhibit antitumor activity, independent of intracellular cAMP levels after transport into nuclei, by arresting the cell cycle at the G$_1$ phase.[1,2] The artificial PG **3**[3] reveals potent antiproliferative and antiviral effects[4] and, therefore, has been utilized as an efficient molecular probe for investigating both the intracellular behavior and the molecular mechanism of biological effects.[2,5] We have recently clarified that the inhibition of the growth of HL-60 human leukemia cells by **3** results mainly from the induction of p21, known as a cyclin-dependent kinase (Cdk) inhibitor regulating the cell cycle progression, via a p53-independent pathway.[5d] The readily accessible PG **3** is now undergoing a preclinical study for the treatment of chemotherapeutically resistant ovarian cancer.[6] While much promising data as an anticancer agent have been accumulated,[2,4−6] unfortunately, **3** and its acid form **2** are rapidly metabolized in rat serum ($t_{1/2}$ < 5 min) via Δ^7-PGC$_1$ (**4**) by the action of PG isomerases, as shown in Scheme 1.[7] Natural PGA$_1$ (**5**), which expresses similar but weaker antitumor activity, is even less stable ($t_{1/2}$ < 1 min) in serum, giving PGC$_1$ and then PGB$_1$.[7,8] Thus it is a central problem to overcome this biological instability of **2** in order to create efficient chemotherapeutic agents. Described herein is the development of antitumor PGs with high biological stability and improved cell growth inhibition.



Scheme 1. Metabolic Pathway of Δ^7-PGA$_1$ Methyl Ester (**3**) and PGA$_1$ (**5**) in the Serum



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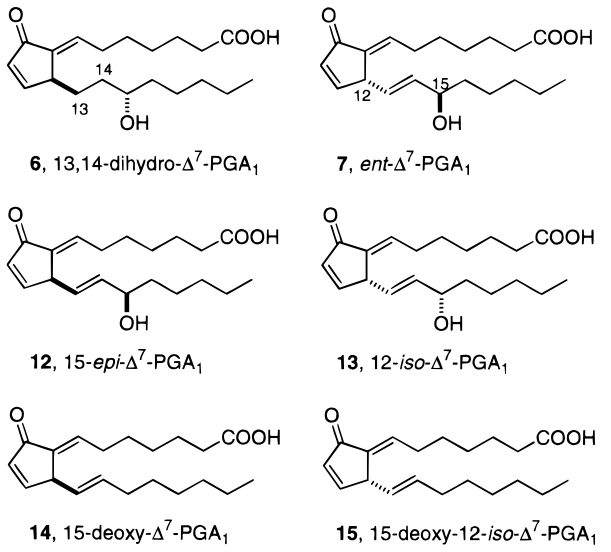
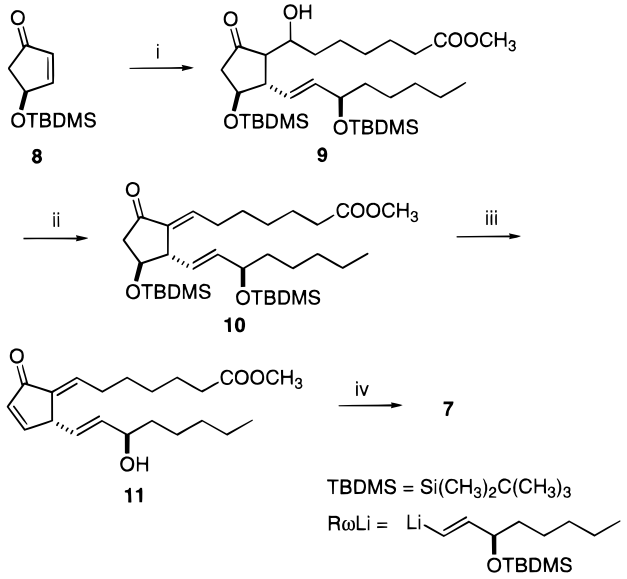
Results and Discussion

Metabolic conversion of endogenous substances is generally thought to occur through strict molecular recognition between the substrate and the targeting enzyme.[9] The more facile metabolism of PGA_1 to PGC_1 than that of Δ^7-PGA_1 (**2**) suggests a higher degree of enzymatic recognition for the structure of PGA_1 than for Δ^7-PGA_1. As such, we first paid attention to 13,14-dihydro-Δ^7-PGA_1 (**6**), because the saturation of the C(13)−C(14) double bond changes the spatial arrangement of the ω-side chain,[10] potentially reducing the molecular recognition by the enzyme and also destabilizing the C-type metabolite in comparison to **4** by a partial loss of π-conjugation. In fact, the ω-chain-saturated derivative **6** exhibited a much higher stability ($t_{1/2}$ = 92 min) than **2** in the rat serum, but unfortunately, its antiproliferative activity was considerably weaker, the IC_{50} value for colon 26 cancer cells being 8-fold larger than that of **2**.[11]



Molecular chirality furnishes a straightforward solution for this biochemical problem. Δ^7-PGA_1 (**2**) has two stereogenic centers at C(12) and C(15). The C(12) stereochemistry represents a pivotal point in this metabolism because the proton on this carbon is removed during the A- to C-type structural change (Scheme 1), while the C(15) hydroxy group might interact with the enzyme through hydrogen bonding as in the case of hormonal PGs binding with cellular membrane receptors.[12] These considerations have prompted us to investigate the biological property of the antipodal congener of **2**.[13] The antipode of **2**, *ent*-Δ^7-PGA_1 (**7**), was synthesized based on our three-component coupling process[3] as illustrated in Scheme 2. The *R* configuration at C(15) is most conveniently generated by the asymmetric reduction of an enone or an acetylenic ketone.[14] The *R* stereogenic center at C(12) of **7** is created by asymmetric induction during the conjugate addition of the metalated ω-chain unit to the (*S*)-4-hydroxy-2-cyclopentenone derivative **8**.[15] Thus condensation of the in situ generated enolate with the α-chain aldehyde unit afforded the three-component coupling product **9**. Slow addition of **8** into the solution of the metalated ω-chain unit at −78 °C or below is essential for high reproducibility, which was achieved using a specially designed

Scheme 2. Synthesis of *ent*-Δ^7-PGA_1 (**7**)[a]



[a] Reagents: (i) RωLi, $(CH_3)_2Zn$, THF, and then $OHC(CH_2)_5COOCH_3$, 91% yield; (ii) CH_3SO_2Cl, 4-(dimethylamino)pyridine, CH_2Cl_2, 85% yield; (iii) $CH_3COOH-H_2O$, 60 °C, 70% yield; (iv) porcine liver esterase, phosphate buffer (pH 8.0)−acetone, 99% yield.

ampule with a spiral tube.[16] The aldol adduct **9** was dehydrated by the mesylation-elimination sequence to give the α,β-enone **10**. Deprotection of the silyl ether and subsequent dehydration at the cyclopentanone ring under acidic conditions gave the cross-conjugated dienone **11**. Finally, *ent*-Δ^7-PGA_1 (**7**) was obtained by enzymatic hydrolysis of the ester **11** with porcine liver esterase.

In fact, introduction of an unnatural configuration into the enzyme-targeting site produced a stable antitumor PG that retained the antiproliferative activity of the cross-conjugated dienone **2**. The time courses of the metabolic decay of the enantiomeric PGs, **2** and **7**, in the rat serum at 37 °C are compared in Figure 1A.[7] The antipode **7** exhibited a remarkably longer half-life ($t_{1/2}$ = 71 min) than **2** ($t_{1/2}$ < 5 min). Since these compounds have the same chemical properties, the above discrimination is due to differences in their recognition by the isomerases.

We next directed our attention to learning about the relative importance of the two stereocenters, C(12) and C(15), for the enhancement of the biological stability. Although the *S* configuration at C(15) plays a key role in the biological activities of PGs through signal transduction initiated by the binding of PGs with cellular membrane receptors,[17] little is known about the structure−stability relationship in the metabolism of antitumor PGs.[4] In this respect, we synthesized the diastereomer **12** and its enantiomer **13**[4] as well as the enantiomeric 15-deoxy derivatives **14** and **15**, particularly focusing on the C(12) stereocenter.[18]

The stability of these compounds in rat serum is summarized in Figure 1B. The 15-deoxy compound **14**, having the same C(12) absolute configuration as **2**, easily underwent metabolism in a short period ($t_{1/2}$ = 3 min), whereas the 15-deoxy-12-*iso* isomer **15**, having the opposite C(12) geometry, was significantly resistant to enzymatic isomerization ($t_{1/2}$ = 55 min). The antipode

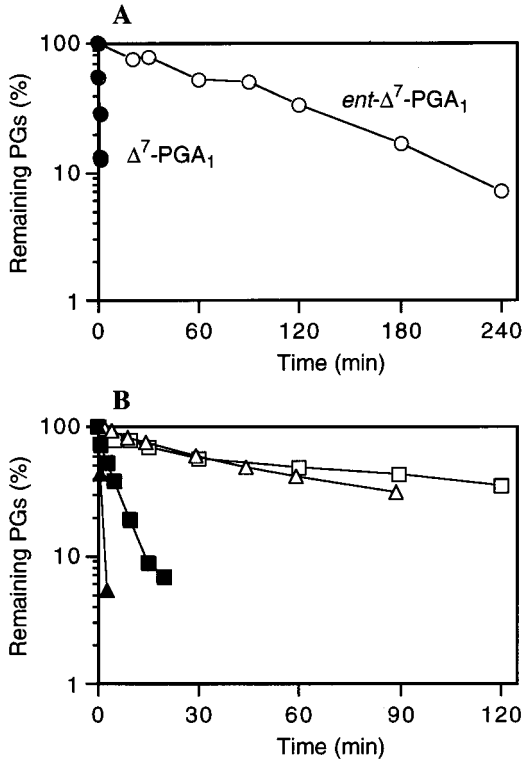


Figure 1. (A) Metabolic decay of Δ^7-PGA_1 (**2**) and *ent*-Δ^7-PGA_1 (**7**) in the rat serum at 37 °C. (B) Metabolic decay of PGs (▲, **12**; △, **13**; ■, **14**; □, **15**) in the rat serum at 37 °C.

7, possessing the *R* configuration at C(15) ($t_{1/2} = 71$ min, Figure 1A), was slightly more stable than **15**, and the 15*S*-configured compound **2** ($t_{1/2} < 1$ min) was in turn slightly less stable than **14**. 15-*epi*-Δ^7-PGA_1 (**12**, $t_{1/2} <$ 1 min) and 12-*iso*-Δ^7-PGA_1 (**13**, $t_{1/2} = 46$ min) enjoyed a stability comparable with that of **2** and **7**, respectively. These results conclude that *the stability of PGAs in rat serum is crucially controlled by the C(12) configuration and is unaffected by the geometry of the hydroxy-bearing C(15)*.[19]

The observed stability of the PGs in rat serum was then compared with their chemical stability. The cross-conjugated dienone **2** was more sensitive to basic conditions than the enone **5**.[7] Thus treatment of **2** with excess triethylamine in dichloromethane at ambient temperature induced a selective transformation to the C-type structure **4**, while the enone **5** was stable under such conditions. The chemical instability of **2** is attributed to the characteristic triply allylic structure centered at C(12). The C(12) proton of **2** is kinetically activated by the adjacent three olefinic bonds to be more acidic than an ordinary methine, thus leading to a highly delocalized anion. The conversion of **2** to **4** would also be more facile than of PGA_1 to PGC_1 on thermodynamic grounds, in accord with a MO calculation[20] suggesting that the model conversion of **16** to **17** is more exothermic ($\Delta H = -2.96$ kcal/mol) than the transformation of **18** to **19** ($\Delta H = -1.27$ kcal/mol). The chemical behavior of the PGs under abiological conditions agrees with such a consideration. In rat serum, however, the natural enone **5** undergoes metabolism much more rapidly than the artificial dienone **2**, indicating that the biological conversion is kinetically facilitated, whereas enzymatic molecular recognition overwhelms the chemical properties of the substrates in an achiral environment.

Table 1. Antiproliferative Activity of PGs for Colon 26 Cancer Cells

prostaglandin	configurations C(12)	C(15)	IC_{50} (μg/mL)
Δ^7-PGA_1 (**2**)	*S*	*S*	0.57
ent-Δ^7-PGA_1 (**7**)	*R*	*R*	0.50
12-*iso*-Δ^7-PGA_1 (**13**)	*R*	*S*	0.35
15-deoxy-12-*iso*-Δ^7-PGA_1 (**15**)	*R*		0.23

Table 2. Growth Inhibition of A172 Human Glioma Cells by Antitumor Prostaglandins

prostaglandin	inhibition period (h)[a]
Δ^7-PGA_1 methyl ester	<48
ent-Δ^7-PGA_1 methyl ester	>72
12-*iso*-Δ^7-PGA_1 methyl ester	>72
15-deoxy-12-*iso*-Δ^7-PGA_1 methyl ester	<24
PGA_2	<24
PGJ_2	<24

[a] The time for the cell growth being suppressed without exceeding the initial cell numbers after treatment with each PG (5 μM).

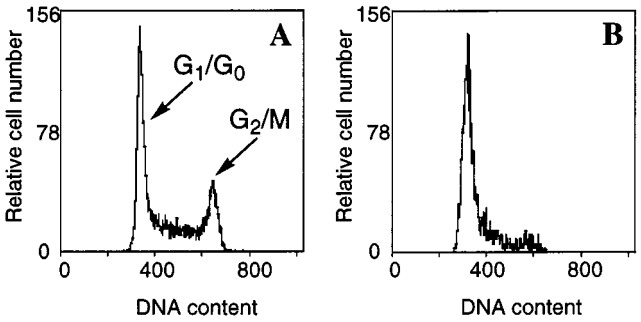
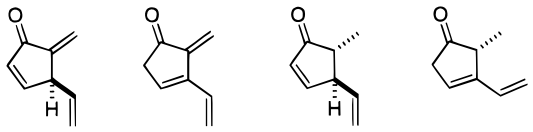


Figure 2. Cell cycle distributions of A172 human glioma cells incubated with *ent*-Δ^7-PGA_1 methyl ester (A, control; B, treated with 5 μM PG).



The metabolically stable PGs, **7**, **13**, and **15**, possessing the unnatural configurations at C(12) exhibit potent antiproliferative activities for colon 26 cancer cells as shown in Table 1. Moreover the C(15)-hydroxy exerts little effect since both *R* and *S* epimers are equipotent and the C(15)-deshydroxy analogue shows slightly enhanced potency. Notably, the biological characteristics of compounds **7** and **13** are much more conspicuous at the molecular level in comparison to those of PGA_2, PGJ_2, or **2** having natural configurations.[21] In particular, they exhibit a long-term potent antiproliferative effect[22] for human glioma cells (Table 2) and strongly increased induction of p21[23] leading to sharp cell cycle arrest at the G_1 phase for the same leukemia cells without causing cell death (Figure 2).[21] Δ^7-PGA_1 methyl ester (**3**), PGA_2, PGJ_2, and **15** scarcely exert any cell cycle arrest at such a low dose level (5 μM).

Conclusion

This study elucidated the structural origin of the instability of **2** in sera. Introduction of the unnatural configuration into the isomerase-sensitive stereocenter not only overcame the metabolic instability but also increased the activity for the induction of p21 leading to cell cycle arrest at the G_1 phase. Such chiral PGs are readily accessible by the three-component synthesis[3] aided by the multikilogram-scale asymmetric synthesis of **8**.[15] The successful design of antitumor PGs resistant to enzymatic metabolism demonstrates the efficacy of research, directed from the in vitro molecular level to the in vivo system, to create useful PGs for cancer chemotherapy.

Experimental Section

General. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates (silica gel 60 F_{254}, 0.25 mm, Merck 5715). Column chromatography was carried out on Merck silica gel 60 (Art. 9385, 230−400 mesh), Fuji Devison BW-820-MH (70−200 mesh), or Fuji Devison BW-300 (200−400 mesh). Preparative TLC was performed on precoated silica gel plates (silica gel 60 F_{254}, 0.5 mm, Merck 5744). Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a JEOL JNM-A400, GX-270, or GSX-270 spectrometer. Chemical shifts are reported in parts per million (δ) with tetramethylsilane in $CDCl_3$ or the deuterium lock signal of $CDCl_3$ as the internal standard. Optical rotations were measured in $CHCl_3$ or methanol at the sodium D line on a JASCO DIP-181 or HORIBA SEPA-300 instrument.

Unless otherwise noted, reagents used were in commercial grade. Tetrahydrofuran (THF) was freshly distilled from sodium-benzophenone ketyl. Dichloromethane and triethylamine were freshly distilled over CaH_2 prior to use. Porcine liver esterase (suspension in 3.2 M ammonium sulfate solution, pH 8.0) was purchased from Sigma. All chemical reactions were performed under a positive pressure of argon. Δ^7-PGA_1 methyl ester (**3**) was synthesized by the three-component coupling process described previously.[3] Hydrolysis of **3** to the acid form **2** was conducted with porcine liver esterase in a mixture of phosphate buffer and acetone.

Preparation of (*R*,*E*)-3-(*tert*-Butyldimethylsiloxy)-1-iodo-1-octene (ω-Chain Precursor). To a solution of (*R*)-1-octyn-3-ol (Aldrich, >99% optical purity; 2.88 g, 22.8 mmol) in dichloromethane (50 mL) were added imidazole (2.80 g, 41.1 mmol) and *tert*-butylchlorodimethylsilane (4.10 g, 27.2 mmol). The reaction mixture was stirred for 21 h at ambient temperature and then poured into aqueous HCl (1 M). The product was extracted with hexane, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (hexane) to give (*R*)-3-(*tert*-butyldimethylsiloxy)-1-octyne[24] (5.26 g, 96%): TLC R_f = 0.35 (hexane); bp 79−85 °C at 3 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.13 (s, 3H), 0.84−1.00 (12H), 1.25−1.50 (6H), 1.60−1.72 (m, 2H), 2.37 (d, J = 1.7 Hz, 1H), 4.25−4.45 (m, 1H).

Freshly distilled (*R*)-3-(*tert*-butyldimethylsiloxy)-1-octyne (1.95 g, 8.11 mmol) dissolved in dichloromethane (50 mL) was added to a solution of chlorobis(cyclopentadienyl)hydridozirconium (4.60 g, 17.8 mmol) in dichloromethane at ambient temperature, and the resulting mixture was stirred for 15 min and then cooled to 0 °C. To this was added a solution of iodine (2.26 g, 8.90 mmol) in dichloromethane (50 mL) dropwise with stirring. The mixture was further stirred at ambient temperature for 15 min and then poured into aqueous sodium thiosulfate (10%). The product was extracted with hexane, and the resulting extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was subjected to column chromatography on silica gel (hexane) to afford (*R*,*E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-1-octene (2.56 g, 86%): TLC R_f = 0.51 (hexane); bp 114−120 °C at 6 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.02 (s, 3H), 0.00 (s, 3H), 0.80−0.90 (12H), 1.15−1.50 (6H), 3.98−4.08 (m, 1H), 6.14 (dd, J = 1.2, 14.4 Hz, 1H), 6.47 (dd, J = 6.1, 14.4 Hz, 1H); $[\alpha]^{25.8}_D$ +36.4 (*c* 1.00, methanol) (*S* isomer: $[\alpha]^{23}_D$ −37.5 (*c* 0.97, methanol)).[3b]

Synthesis of *ent*-Δ^7-PGA_1 (7). Freshly distilled (*R*,*E*)-3-(*tert*-butyldimethylsilyl)-1-iodo-1-octene (2.15 g, 5.84 mmol) was placed in an ampule with a spiral tube[16] and dissolved in THF (40 mL). After the solution was cooled to −98 °C, *tert*-butyllithium (1.89 M pentane solution, 6.18 mL, 11.7 mmol) was added, and the solution was stirred at −98 °C for 15 min. To this was added $Zn(CH_3)_2$ (1.0 M hexane solution, 5.84 mL, 5.84 mmol), and the mixture was warmed to 0 °C, stirred for 20 min, and cooled again to −98 °C. Then, a solution of (*S*)-4-(*tert*-butyldimethylsiloxy)-2-cyclopenten-1-one (**8**) (1.23 g, 5.80 mmol) in THF (55 mL) was added to the mixture at −98 °C over a period of 2 h through the spiral tube. After the mixture was stirred at −98 °C for 20 min, a solution of methyl 6-formylhexanoate (918 mg, 5.80 mmol) in THF (40 mL) was added over a period of 20 min, and the solution was stirred at the same temperature for 20 min. The reaction mixture was poured into saturated aqueous NH_4Cl solution (200 mL), and the mixture was extracted with hexane (200 mL × 4). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (5:1 hexane/ethyl acetate) to afford the coupling product **9** (3.22 g, 91%) as a colorless oil: TLC R_f = 0.37 (4:1 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.03 (s, 3H), −0.01 (s, 3H), 0.01 (s, 3H), 0.03 (s, 3H), 0.84−0.85 (21H), 1.2−1.6 (16H), 2.02 (dd, J = 5.4, 7.9 Hz, 1H), 2.25 (t, J = 7.4 Hz, 2H), 2.27 (dd, J = 6.4, 17.8 Hz, 1H), 2.64 (dd, J = 6.4, 17.8 Hz, 1H), 2.6−2.7 (m, 1H), 3.29 (br, 1H), 3.61 (s, 3H), 3.69 (q, J = 5.9 Hz, 1H), 4.05 (q, J = 6.4 Hz, 1H), 5.33 (dd, J = 7.9, 15.3 Hz, 1H), 5.58 (dd, J = 4.5, 15.3 Hz, 1H).

To a solution of the alcohol **9** (1.53 g, 2.50 mmol) in dichloromethane (60 mL) were added 4-(dimethylamino)-pyridine (2.44 g, 20.0 mmol) and methanesulfonyl chloride (774 μL, 10.0 mmol) at ambient temperature. After the mixture was stirred for 15 h, aqueous HCl solution (0.2 M, 60 mL) was introduced. The organic layer was separated and washed with brine, and the aqueous layer was extracted with ethyl acetate (30 mL × 4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate, 10:1) to give the enone **10** (1.26 g, 85%): TLC R_f = 0.56 (4:1 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.02 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.8−0.9 (21H), 1.2−1.7 (14H), 2.10 (q, J = 6.9 Hz, 2H), 2.23 (d, J = 17.8 Hz, 1H), 2.29 (t, J = 7.9 Hz, 2H), 2.49 (dd, J = 5.0, 17.8 Hz, 1H), 3.42 (d, J = 5.9 Hz, 1H), 3.66 (s, 3H), 4.03 (q, J = 5.4 Hz, 1H), 4.19 (q, J = 5.0 Hz, 1H), 5.40 (dd, J = 5.9, 15.8 Hz, 1H), 5.52 (dd, J = 5.9, 15.8 Hz, 1H), 6.72 (dt, J = 1.5, 5.9 Hz, 1H).

The enone **10** (187 mg, 0.314 mmol) was dissolved in a THF/CH_3COOH/H_2O mixture (1:2:1, 10 mL), and the solution was heated at 70 °C for 16 h. After the mixture was cooled to ambient temperature, saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the resulting mixture was extracted with ethyl acetate (20 mL × 4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (3:1 hexane/ethyl acetate) to afford *ent*-Δ^7-PGA_1 methyl ester (**11**) (76.3 mg, 70%): TLC R_f = 0.38 (1:1 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 3H), 1.3−1.7 (14H), 2.1−2.3 (m, 2H), 2.30 (t, J = 7.4 Hz, 2H), 3.66 (s, 3H), 4.02 (d, J = 6.4 Hz, 1H), 4.10 (q, J = 6.4 Hz, 1H), 5.44 (dd, J = 8.4, 16.3 Hz, 1H), 5.70 (dd, J = 6.4, 15.3 Hz, 1H), 6.33 (dd, J = 2.0, 5.9 Hz, 1H), 6.60 (t, J = 7.9 Hz, 1H), 7.36 (dd, J = 2.0 Hz, 1H).

To a solution of the methyl ester **11** (7.2 mg, 21 μmol) in acetone (0.2 mL) were added phosphate buffer (pH 8.0, 2.0 mL) and porcine liver esterase (suspension in 3.2 M ammonium

sulfate solution, 100 μL) at ambient temperature, and the mixture was stirred for 4 h. Then, the solution was acidified with diluted HCl solution (0.1 M) to pH 4, and the resulting mixture was extracted with ethyl acetate (3 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. The residual oil was subjected to preparative TLC using a 10:1 mixture of dichloromethane and methanol as eluent to give *ent*-Δ^7-PGA$_1$ (**7**) (7.1 mg, 99%): TLC R_f = 0.49 (10:1 dichloromethane/methanol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3H), 1.2−1.7 (14H), 2.1−2.3 (m, 2H), 2.33 (t, J = 7.4 Hz, 2H), 4.02 (d, J = 7.4 Hz, 1H), 4.11 (q, J = 6.4 Hz, 1H), 5.47 (dd, J = 8.9, 15.4 Hz, 1H), 5.70 (dd, J = 6.4, 15.4 Hz, 1H), 6.34 (dd, J = 1.8, 5.8 Hz, 1H), 6.61 (t, J = 7.4 Hz, 1H), 7.37 (dd, J = 2.0, 5.8 Hz, 1H); $[\alpha]^{25}_D$ −198.5 (*c* 0.695, $CHCl_3$) (**2**: $[\alpha]^{25}_D$ +203.7 (*c* 0.755, $CHCl_3$)).

15-*epi*-Δ^7-PGA$_1$ (12). The synthesis of **12** was carried out according to the procedure for the synthesis of **7** except for the use of (*R*)-4-(*tert*-butyldimethylsiloxy)-2-cyclopenten-1-one (**20**). **12**: TLC R_f = 0.49 (10:1 dichloromethane/methanol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 3H), 1.3−1.7 (14H), 2.1−2.3 (m, 2H), 2.33 (t, J = 7.4 Hz, 2H), 4.03 (d, J = 8.4 Hz, 1H), 4.10 (q, J = 6.4 Hz, 1H), 5.41 (dd, J = 8.4, 15.3 Hz, 1H), 5.71 (dd, J = 6.4, 15.3 Hz, 1H), 6.34 (dd, J = 2.0, 5.9 Hz, 1H), 6.62 (t, J = 7.9 Hz, 1H), 7.34 (dd, J = 2.5, 5.9 Hz, 1H); $[\alpha]^{23}_D$ +178.0 (*c* 0.592, $CHCl_3$).

12-*iso*-Δ^7-PGA$_1$ (13). The synthesis of **13** was carried out according to the procedure for the synthesis of **7** except for the use of (*S*,*E*)-3-(*tert*-butyldimethylsilyl)-1-iodo-1-octene. **13**: TLC R_f = 0.49 (10:1 dichloromethane/methanol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 3H), 1.3−1.7 (14H), 2.1−2.3 (m, 2H), 2.33 (t, J = 7.4 Hz, 2H), 4.03 (d, J = 8.4 Hz, 1H), 4.10 (q, J = 6.4 Hz, 1H), 5.41 (dd, J = 8.4, 15.3 Hz, 1H), 5.71 (dd, J = 6.4, 15.3 Hz, 1H), 6.34 (dd, J = 2.0, 5.9 Hz, 1H), 6.62 (t, J = 7.9 Hz, 1H), 7.34 (dd, J = 2.5, 5.9 Hz, 1H); $[\alpha]^{24}_D$ −177.9 (*c* 0.535, $CHCl_3$).

15-Deoxy-Δ^7-PGA$_1$ (14). The synthesis of **14** was carried out according to the procedure for the synthesis of **7** except for the use of **20** and (*E*)-1-iodo-1-octene as a side-chain precursor. **14**: TLC R_f = 0.52 (10:1 dichloromethane/methanol);^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, J = 6.4 Hz, 3H), 1.2−1.6 (14H), 2.01 (q, J = 6.4 Hz, 2H), 2.1−2.3 (m, 2H), 2.34 (t, J = 7.4 Hz, 2H), 3.97 (d, J = 6.9 Hz, 1H), 5.16 (dd, J = 8.4, 14.8 Hz, 1H), 5.65 (dt, J = 6.4, 14.8 Hz, 1H), 6.31 (dd, J = 2.0, 5.9 Hz, 1H), 6.59 (t, J = 7.4 Hz, 1H), 7.35 (dd, J = 2.5, 5.0 Hz, 1H); $[\alpha]^{24.5}_D$ +169 (*c* 0.72, $CHCl_3$).

15-Deoxy-12-*iso*-Δ^7-PGA$_1$ (15). The synthesis of **15** was carried out according to the procedure for the synthesis of **7** except for the use of (*E*)-1-iodo-1-octene as ω-chain precursor. **15**: TLC R_f = 0.52 (10:1 dichloromethane/methanol);^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, J = 6.4 Hz, 3H), 1.2−1.6 (14H), 2.01 (q, J = 6.4 Hz, 1H), 2.1−2.3 (m, 2H), 2.34 (t, J = 7.4 Hz, 2H), 3.97 (d, J = 6.9 Hz, 1H), 5.16 (dd, J = 8.4, 14.8 Hz, 1H), 5.65 (dt, J = 6.4, 14.8 Hz, 1H), 6.31 (dd, J = 2.0, 5.9 Hz, 1H), 6.59 (t, J = 7.4 Hz, 1H), 7.35 (dd, J = 2.5, 5.0 Hz, 1H); $[\alpha]^{24.5}_D$ −169.6 (*c* 0.640, $CHCl_3$).

Synthesis of 13,14-Dihydro-Δ^7-PGA$_1$ (6). A mixture of **21** (348 mg, 0.568 mmol), an intermediate in the synthesis of **3**,[3] and PtO_2 (8.0 mg) in ethanol (10 mL) was stirred at ambient temperature for 14 h under H_2 atmosphere. Then, the reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (12:1 hexane/ethyl acetate) to give the 13,14-dihydro derivative **22** (348.5 mg, 99%): TLC R_f = 0.39 (4:1 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.07 (s, 3H), 0.1 (s, 3H), 0.8−0.9 (21H), 1.3−1.7 (20H), 1.95 (q, J = 4.5 Hz, 1H), 2.04 (br, 1H), 2.23 (d, J = 17.8 Hz, 1H), 2.31 (t, J = 7.4 Hz, 2H), 2.55 (dd, J = 5.4, 17.8 Hz, 1H), 3.6−3.7 (m, 1H), 3.66 (s, 3H), 3.76 (q, J = 5.5 Hz, 1H), 3.89 (d, J = 2.0 Hz, 1H), 4.1−4.2 (m, 1H).

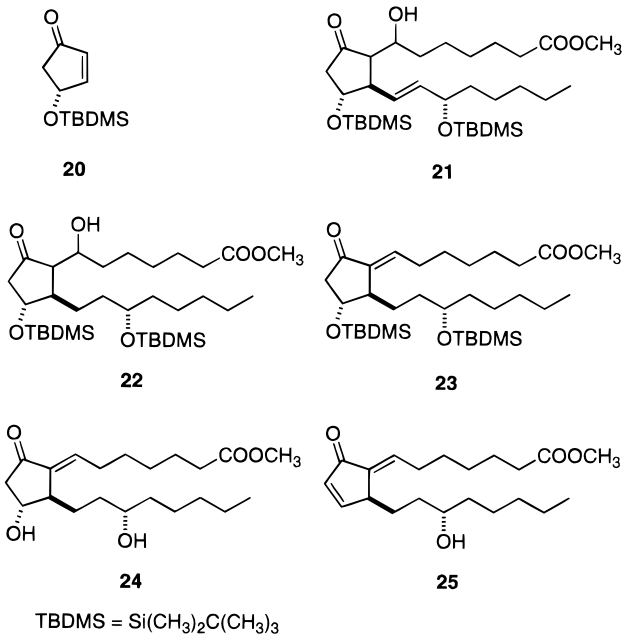
To a solution of **22** (348 mg, 0.566 mmol) in dichloromethane (6 mL) were added methanesulfonyl chloride (65 μL, 0.84 mmol) and 4-(dimethylamino)pyridine (208 mg, 1.70 mmol) at ambient temperature. After the mixture had stirred for 16 h, additional methanesulfonyl chloride (70 μL, 0.9 mmol) and 4-(dimethylamino)pyridine (201 mg, 1.64 mmol) were added to the reaction mixture, and the stirring was continued for 5 h. Then, aqueous HCl solution (5%, 10 mL) was added to the mixture. The organic layer was separated and washed with brine (5 mL), and the aqueous layer was extracted with ethyl acetate (5 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (15:1 hexane/ethyl acetate) to give the enone **23** (248 mg, 73%): TLC R_f = 0.53 (4:1 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.02 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.8−0.9 (21H), 1.3−1.7 (18H), 2.15 (q, J = 7.4 Hz, 2H), 2.23 (d, J = 18.3 Hz, 1H), 2.29 (t, J = 7.4 Hz, 2H), 2.54 (dd, J = 4.9, 18.3 Hz, 1H), 2.72 (br, 1H), 3.61 (m, 1H), 3.65 (s, 3H), 4.22 (d, J = 5.0 Hz, 1H), 6.59 (t, J = 7.4 Hz, 1H).

A mixture of aqueous HF (47%, 0.1 mL) and acetonitrile (0.9 mL) was added to a solution of the enone **23** (24.5 mg, 41 μmol) in acetonitrile (1.5 mL) at 0 °C. After the mixture was stirred for 30 min, additional aqueous HF and acetonitrile (1:9, 1.0 mL) were added, and the stirring was continued for 90 min at the same temperature. To this was added saturated aqueous $NaHCO_3$ (4.0 mL), and the mixture was extracted with ethyl acetate (4 mL × 4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (1:1 hexane/ethyl acetate) to afford the desilylated product **24** (14.2 mg, 94%): TLC R_f = 0.35 (1:3 hexane/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3H), 1.2−1.9 (18H), 2.1−2.4 (5H), 2.66 (dd, J = 5.4, 18.3 Hz, 1H), 2.91 (m, 1H), 3.61 (br, 1H), 3.66 (s, 3H), 4.35 (d, J = 5.0 Hz, 1H), 6.65 (t, J = 7.4 Hz, 1H).

To a solution of the methyl ester **24** (12.1 mg, 32.8 μmol) and 4-(dimethylamino)pyridine (50 mg, 0.41 mmol) in dichloromethane (1.5 mL) was slowly added trifluoroacetic anhydride (23 μL, 0.16 mmol) at 0 °C, and the mixture was stirred at the same temperature for 20 min. Then the reaction was quenched with saturated aqueous $NaHCO_3$ (1.5 mL), and the mixture was extracted with ethyl acetate (1 mL × 3). The organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. The resulting crude product (14 mg) was dissolved in THF (1.5 mL) and mixed with saturated aqueous $NaHCO_3$ (1.5 mL). The reaction mixture was stirred at ambient temperature for 1.5 h and diluted with brine (1.0 mL). The mixture was extracted with ethyl acetate (1 mL × 4), and the combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (4:1 hexane/ethyl acetate) to give the dienone **25** (10.3 mg, 90%): TLC R_f = 0.52 (1:1 hexane/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.2−1.7 (16H), 1.7−1.8 (m, 1H), 1.8−1.9 (m, 1H), 2.1−2.4 (m, 2H), 2.30 (t, J = 7.3 Hz, 2H), 3.53 (dd, J = 2.4, 4.4 Hz, 1H), 3.56 (tt, J = 5.4, 7.3 Hz, 1H), 3.66 (s, 3H), 6.34 (dd, J = 2.0 Hz, 1H), 6.54 (t, J = 7.4 Hz, 1H), 7.52 (dd, J = 2.4, 5.9 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 22.6, 24.6, 25.3, 28.1, 28.2, 28.8, 31.6, 31.8, 33.0, 33.9, 37.7, 42.9, 51.6, 71.5, 135.1, 135.7, 137.7, 161.7, 174.2, 196.9.

To a solution of the methyl ester **25** (6.6 mg, 18.8 μmol) in acetone (0.2 mL) were added phosphate buffer (pH 8.0, 2.1 mL) and porcine liver esterase (suspension in a 3.2 M ammonium sulfate solution, 60 μL) at ambient temperature, and the mixture was stirred for 8 h. Then the solution was acidified with diluted HCl solution (0.1 M) to pH 4, and the mixture was extracted with ethyl acetate (2 mL × 3). The organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. The residual oil was subjected to preparative TLC using a 10:1 mixture of dichloromethane and methanol as eluent to give 13,14-dihydro-Δ^7-PGA$_1$ (**6**) (5.5 mg, 87%): TLC R_f = 0.49 (10:1 dichloromethane/methanol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 3H), 1.2−1.7 (16H), 1.7−2.0 (m, 2H), 2.2−2.4 (m, 2H), 2.35 (t, J = 7.4 Hz, 2H), 3.5−3.6

(m, 2H), 6.35 (dd, J = 2.0, 5.9 Hz, 1H), 6.55 (t, J = 7.4 Hz, 1H), 7.52 (dd, J = 2.5, 5.9 Hz, 1H).



Metabolic Decay of PGs in the Rat Serum. An ethanolic solution of each PG (1 mg/mL, 40 μL) was incubated with the rat serum (760 μL) at 37 °C, and the time course (40-μL sampling) of the substrate disappearance was monitored by HPLC analysis of the supernatant after deproteination with methanol (200 μL) followed by centrifugation. HPLC analyses were performed on a reversed-phase column eluting with a mixture of methanol and acetic acid buffer (0.02 M, pH 5.0).

Growth Inhibition of A172 Cells by PGs and Cell Cycle Analysis. A172 human glioma cells were treated with each PG (5 μM) under standard tissue culture conditions, and the cell numbers were counted by a cell counter for a period of 72 h. Cell cycle distributions were analyzed by flow cytometry after treatment with each PG (5 μM) for 24 h.[21]

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