and FcB1-Columbia are chloroquine-resistant (CI_{50} of chloroquine > 100 nM).[14, 15] Biological activities were measured by the method of Desjardins et al.[16] Assays were performed in triplicate in 96-microplates, cultures being at 1% of hematocrite and with 0.5 – 1% of parasitemia.

For each assay, parasites were incubated with decreasing concentrations of drugs during 32 h (data not shown) or 72 h (four wells contained chloroquine as reference). The initial drug dilutions were made at 10 mg mL^{-1} in dimethylsulfoxide and the next ones with RPMI 1640. The parasite growth was measured by incorporation of tritiated hypoxanthine and compared with the incorporation in the absence of drug (used as 100% value).[17] IC_{50} values were determined by tracing the percentage of inhibition as function of the drug concentration. The IC_{50} values measured at 32 h correspond to the action of the drug on the trophozoite stage and IC_{50} values measured at 72 h (time for 1.5 parasite life cycles) indicate a possible effect on the liberation and reinvasion steps of the erythrocytes by the parasites.

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Designed Prostaglandins with Neurotrophic Activities

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KEYWORDS:

drug research · neurochemistry · prostaglandins · structure – activity relationships · synthesis design

Cyclopentenone prostaglandins (PGs), such as PGA_2 and Δ^{12}-PGJ_2, are recognized as important biosignaling molecules. They participate in cell growth regulation, cell differentiation, and inflammation processes by modulating the expression of a variety of genes and the function of proteins, according to the structures and the cell types in which the latter are found.[1] We previously demonstrated that Δ^7-PGA_1 methyl ester (**1**) and its analogues suppress the growth of glioma cells at the G1 phase of the cell cycle by inducing the expression of cyclin-dependent kinase inhibitor p21 and reducing cyclin E expression.[2] Interestingly, we observed that some Δ^7-PGA_1 methyl ester derivatives caused morphological changes as well as growth arrest in glioma cells, which are typical brain tumor cells, during the study of the antiproliferative effects of these compounds;[3] this suggests that the cells were differentiated by the PGs. In addition, oligomers of PGB_1 derivatives reportedly exhibited neuroprotective activities in cerebral ischemia.[4] However, there has been little information on the actions of structurally defined cyclopentenone PGs in neuronal cells in spite of the abundant distribution of their precursors and PG synthases in the brain.[5] We have been intrigued with examining the effects of cyclopentenone PGs on a standard neuronal cell line, and recently found that natural Δ^{12}-PGJ_2 and its dehydrated derivative 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**2**), which possess a cross-conjugated dienone structure, promoted neurite outgrowth in the presence of nerve growth factor (NGF) in PC12 cells.[6] Based on the extensive study of these natural PGs, we describe here the successful design and

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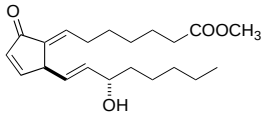
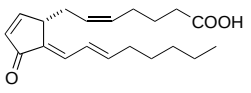


1, Δ^7-PGA$_1$ methyl ester



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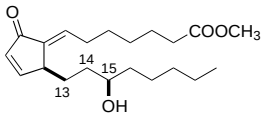
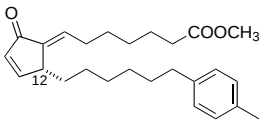


3, 13,14-dihydro-15-*epi*-Δ^7-PGA$_1$ methyl ester

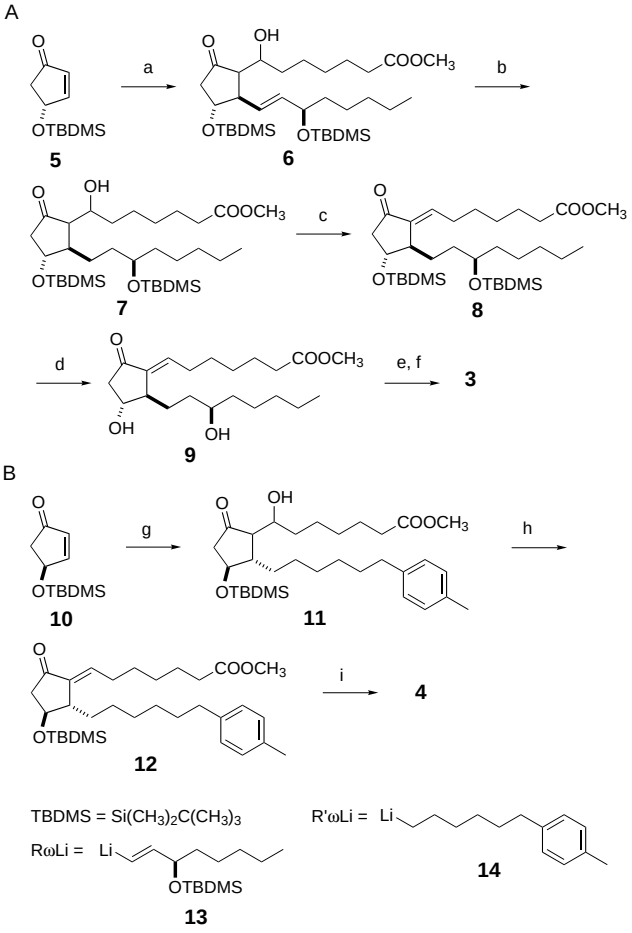


4, 15-deoxy-13,14-dihydro-19,20-dinor-12-*iso*-18-(4-methylphenyl)-Δ^7-PGA$_1$ methyl ester

synthesis of stable PGs, **3** and **4**, with distinct neuroprotective activities.

The cyclopentenone PG derivative **3** has an analogous structure to **1** except for the unnatural configuration at C15 and the saturated bond at C13–C14. This structure was planned to avoid an intrinsic biodegradation of natural PGs.[7, 8] Scheme 1 A illustrates the synthetic pathway to **3**. Thus, the organozincate-mediated three-component coupling reaction of **5**, **13**, and methyl 7-oxoheptanoate gave the adduct **6**,[9] which was then subjected to hydrogenation with platinum oxide to afford the 13,14-dihydro derivative **7**.[7b] Dehydration of **7** with methanesulfonyl chloride in the presence of 4-(dimethylamino)pyridine followed by desilylation with aqueous HF produced the enone **9**. Finally, the 11-hydroxy group of **9** was selectively dehydrated by the combination of trifluoroacetylation and base-catalyzed elimination. During this process, the 15-hydroxy group was also trifluoroacetylated, but the resulting ester was readily hydrolyzed with aqueous sodium bicarbonate, giving the desired product **3**.[10] Thus, the *R* configuration at C15 of **3** was introduced by the use of the antipode of the natural ω-side-chain unit, and the saturated C13–C14 bond was elaborated by hydrogenation of the aldol intermediate **6** prior to the dehydration step.

The second cyclopentenone derivative, **4**, contains a tolyl group at the terminus of the ω side chain and lacks the 15-hydroxy group and C13–C14 double bond compared with the parent compound **1**. The incorporation of a phenyl ring into the ω side chain is partly intended for the modulation of the molecular lipophilicity and partly for the possible conversion of **4** to a ligand for positron emission tomography.[11] The synthesis of **4** is shown in Scheme 1 B. The three-component coupling of **10**, **14**, and methyl 7-oxoheptanoate afforded the adduct **11**, which was then dehydrated to produce the enone derivative **12**. Finally, the heating of **12** in aqueous acetic acid caused elimination of the 11-hydroxy group to give the dienone **4**.[12] The use of 1-bromo-6-(4-tolyl)hexane as the ω-side-chain unit in the three-component coupling process enabled the single-step construction of the principal structural features. The unnatural *R* configuration at C12, contrary to that in **3**, was induced by the cyclopentenone unit with the 4*S* configuration.[7b] Several analogues with modified ω-side-chain structures (**15** – **30**) were similarly synthesized for structure – activity relationship studies.[13]



Scheme 1. *Synthesis of prostaglandin derivatives **3** and **4**. a) RωLi, $(CH_3)_2Zn$, THF, then methyl 7-oxoheptanoate, 82%; b) H_2, PtO_2, C_2H_5OH, 78%; c) CH_3SO_2Cl, 4-(dimethylamino)pyridine, CH_2Cl_2, 72%; d) HF, CH_3CN/H_2O (6:1), 84%; e) $(CF_3CO)_2O$, 4-(dimethylamino)pyridine, CH_2Cl_2; f) $NaHCO_3$, THF/H_2O (1:1), 67% (over two steps); g) R'ωLi, $(CH_3)_2Zn$, THF, then methyl 7-oxoheptanoate, 55%; h) CH_3SO_2Cl, 4-(dimethylamino)pyridine, CH_2Cl_2, 97%; i) $CH_3COOH/THF/H_2O$ (2:1:1), 70 °C, 67%.*

The biological effects of **3** and **4** on neuronal cells were prominent.[14] Thus, **3** strongly promoted the neurite outgrowth of PC12 cells at a concentration of 0.5 μM after a 24-h incubation in the presence of NGF (Figure 1).[6, 15] The dorsal root ganglion (DRG) neurons of chick embryos treated with **3** and NGF also displayed promoted neurite outgrowth (Figure 2), indicating

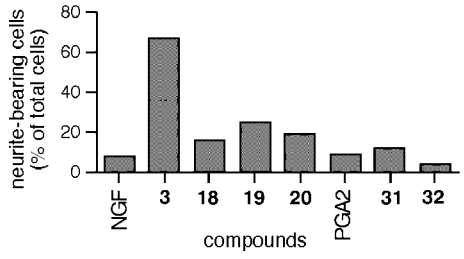


Figure 1. *Promotion of neurite outgrowth by PGs. PC12 cells were incubated with each compound (0.5 μM) in the presence of NGF (50 ng mL^{-1}) for 24 h. The cells with extensions longer than 10 μm were counted as neurite-bearing cells.*

  1439-4227/00/01/04 $ 17.50+.50/0

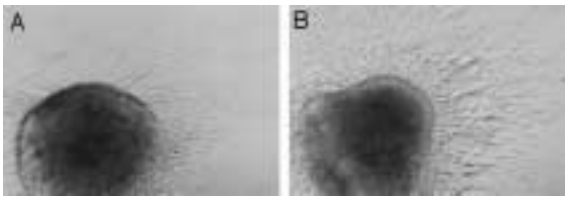
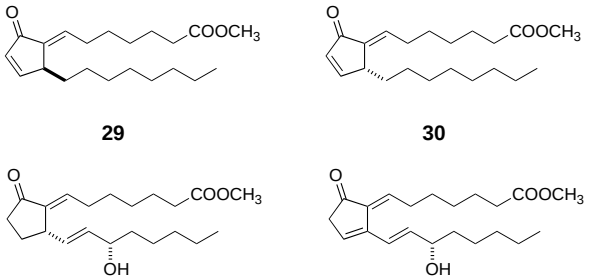


Figure 2. *Promotion of neurite outgrowth from explanted DRG neurons by* ***3****. DRG explant was cultured with NGF (50 ng mL^{-1}) in the absence (A) or presence (B) of* ***3*** *(1.0 μM) for 24 h.*

that the PG affects not only the cultured tumor cell line but also the primary neurons. Moreover, the PG exhibited similar activity even in CAD cells, a central-nervous-system-derived catecholaminergic neuronal cell line.[14] The PGs **1** and **2** and their stereoisomers[13] showed similar effects at a concentration of 0.5 μM against PC12 cells, but their activities markedly decreased at 0.2 μM, whereas **3** maintained comparable potency.[6] At concentrations above 0.5 μM, **2** caused cell death, whereas **3** was not toxic even at more than 5 μM. Δ^7-PGA_1 methyl esters also induced cell death at concentrations of 2 – 5 μM. Interestingly, the other three stereoisomers of **3** at C12 and C15, PGs **18** – **20**,[13] were also less toxic but devoid of neurite-outgrowth-promoting activity (Figure 1). These results indicate that the 13,14 double bond in Δ^7-PGA_1-type compounds plays a pivotal role for their cytotoxicity.[7b] The C15 hydroxy group might modulate the binding of the PG molecule to the target protein but is not an essential structural unit, because 15-deoxy-13,14-dihydro derivatives **29** and **30** promoted neurite outgrowth. Importantly, simple monoenone PGs such as PGA_2, **31**, and **32** with a shifted double bond[7] did not promote neurite outgrowth. This implies that the cross-conjugated dienone structure is crucial for the activity of the PGs (Figure 1).



The prevention of neuronal death is an important issue in geriatric medicine. The designed cyclopentenone **4** prevented the glutamate-induced death of HT22 cells to the extent of $>70\%$ at a concentration of only 0.1 μM.[16] Δ^7-PGA_1 methyl esters and **30** also exhibited similar effects, though less effective than **4**, and, unfortunately, showed higher cell toxicity. The (12*S*)-octyl derivative **29** was moderately active but highly toxic. Other dienone PGs including **2** and the analogues of **4** with a different ω-side-chain length and substitution pattern at the phenyl ring (**21** – **28**)[13] were far less effective. PGA_2, **31**, **32**, and saturated cyclopentanone PGs were completely inert, indicating the requirement of a dienone structure for activity. In addition, **4** was found to promote the neurite outgrowth in PC12 cells at a concentration of 0.1 – 0.5 μM. In contrast, **3**, the most potent promoter of neurite outgrowth among the synthesized PGs, scarcely exhibited the activity for the prevention of neuronal cell death. Thus, **4** is a unique agent comprising dual activities for the promotion of neurite outgrowth and neuronal protection.[17]

Although the intracellular targets of the PGs that are related to their neurotrophic activities have not been identified yet, we obtained evidence that BiP/GRP78, a chaperon protein that is strongly expressed in cells treated with PGs, participated in the signaling cascade leading to the promotion of neurite outgrowth.[14]

We succeeded in developing two novel cyclopentenone prostaglandins with neurotrophic activities by structural modifications of **1**. Thus, the achievement of sharp G1 arrest of tumor cells at less toxic doses by designed PGs has initiated a new phase of PG studies in cell differentiation. These designed stable PGs with low toxicity, which are readily accessible by organic synthesis including the asymmetric synthesis of (*R*)- and (*S*)-4-hydroxy-2-cyclopentenones,[18] provide a firm chemical basis for the design of efficient PG probes that can be used in vivo brain research. They are also potential new chemotherapeutic agents for the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases.

We are grateful to Professor R. Noyori for his continuous encouragement and Professor M. Nakanishi for his initial contribution to this study. This work was supported in part by a Grant-in-Aid for Scientific Research (no. 11358011) from the Ministry of Education, Science, Sports, and Culture of Japan, and by Research for the Future Program (RFTF; no. 98L00201) from the Japan Society for the Promotion of Science.

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[8] Although the ester moiety of **3** will be hydrolyzed to form the corresponding acid, further metabolism to C-type structures by PG isomerases is avoidable.

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[10] Spectroscopic data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.0$ Hz, 3H; CH_3), 1.20 – 1.70 (18H), 2.00 – 2.12 (m, 1H; CH_aH_b), 2.18 – 2.35 (m, 2H; C=CH-CH_2), 2.31 (t, $J = 7.4$ Hz, 2H; CH_2COOCH_3), 3.50 – 3.58 (m, 2H; *CH* and *CH*-OH), 3.67 (s, 3H; $COOCH_3$), 6.35 (dd, $J = 2.0$, 6.0 Hz, 1H; O=C-*CH*=C), 6.55 (t, $J = 7.8$ Hz, 1H; C=*CH*-CH_2), 7.53 (ddd, $J = 0.9$, 2.7, 6.0 Hz, 1H; C=*CH*-CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 14.0$, 22.6, 24.6, 25.3, 28.1, 28.2, 28.8, 28.8, 31.8, 33.0, 33.9, 37.7, 42.9, 51.5, 71.5, 135.1, 135.6, 137.7, 161.6, 174.2, 196.8.

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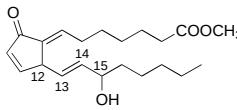
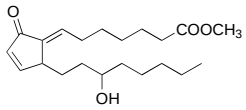
[12] Spectroscopic data for **4**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.18 – 1.70$ (15H), 1.80 (m, 1H; CH_aH_b), 2.24 (m, 2H; C=CH-CH_2), 2.31 (t, $J = 7.4$ Hz, 2H; CH_2COOCH_3), 2.31 (s, 3H; Ar-CH_3), 2.55 (t, $J = 7.8$ Hz, 2H; Ar-CH_2), 3.46 (m, 1H; *CH*), 3.67 (s, 3H; $COOCH_3$), 6.32 (dd, $J = 2.0$, 6.2 Hz, 1H; O=C-*CH*=C), 6.52 (t, $J = 6.8$ Hz, 1H; C=*CH*-CH_2), 7.05 (d, $J = 8.2$ Hz, 2H; Ar-*H*), 7.08 (d, $J = 8.2$ Hz, 2H; Ar-*H*), 7.52 (ddd, $J = 0.8$, 2.5, 6.2 Hz, 1H; C=*CH*-CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 21.0$, 24.7, 25.8, 28.3, 28.9, 28.9, 29.1, 29.7, 31.5, 32.4, 33.9, 35.4, 43.3, 51.5, 128.2 (2C), 128.9 (2C), 134.8, 135.0, 135.2, 138.0, 139.6, 161.9, 174.0, 196.9.

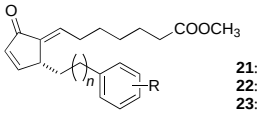
[13] The structures of other Δ^7-PGA_1 derivatives synthesized in this study are listed below.



15: 12*R*, 15*R*
16: 12*S*, 15*R*
17: 12*R*, 15*S*



18: 12*S*, 15*S*
19: 12*R*, 15*R*
20: 12*R*, 15*S*



21: $n = 1$, R = p-CH_3
22: $n = 1$, R = m-CH_3
23: $n = 3$, R = p-CH_3
24: $n = 3$, R = m-CH_3
25: $n = 4$, R = H
26: $n = 5$, R = m-CH_3
27: $n = 6$, R = H
28: $n = 7$, R = p-CH_3

[14] A detailed description of the biological effects will be reported separately.

[15] We refer to these PGs as NEPPs (*NE*urite outgrowth/regeneration-*P*romoting *P*rostaglandins).

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