mechanical models suggest that, unlike linear chains, a two-dimensional polymer network can undergo a low-temperature transition to a flat phase (3). The transformation from smectic layers into the isotropic state may be an experimental manifestation of the so-called "crumpling transition" of a two-dimensional polymer network. Further experimental work will be needed to examine how the bilayer structure actually changes so as to produce an isotropic liquid.

Scale up in materials processing is always a concern because one often finds that the required human assistance to realize ordered materials requires prohibitive cost. High molecular weight in polymers normally limits its solubility and processibility. But these sheet-like gigamolecules are ideal smectogens, forming a relatively low viscosity liquid which can be readily processed into oriented films. Self-assembly of the two-dimensional sheets in bulk followed by thermal- or radiation-induced polymerization-stabilization of the objects appears to avoid such problems. Further processing of the individual sheets into ordered films for a variety of applications is promising, but will require more detailed understanding of the nature of this new structure. Properties that will need characterization include surface and edge energies, mean thickness, roughness, number and type of holes and other defects, curvature, modulus, the nature of the stitching networks, and oligomer conformation. The influence of the stitching temperature and inter-sheet interactions on molecular mobility will be of prime interest concerning the crystal to smectic to isotropic phase transitions and the physical properties that assemblies of such sheets will exhibit.

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Organic Synthesis of Prostaglandins: Advancing Biology

Ryoji Noyori and Masaaki Suzuki

Prostaglandins (PGs), a family of C_{20}-unsaturated polyoxygenated fatty acids, regulate diverse functions of the circulatory and respiratory systems and digestive organs and are also crucial for such vital defense processes as inflammation, tissue repair, and immune responses. In addition, PGs are showing new potential as therapeutic agents with the recent demonstrations of their antineoplastic and sleep-inducing activities. Thus, this intriguing family of substances has attracted broad attention in fields ranging from chemistry and biochemistry to pharmacology and medicine (*1*). Organic synthesis is pivotal in developing such an interdisciplinary scientific endeavor and, in this context, the Corey PG synthesis is a triumph of synthetic organic chemistry (*2*). This pioneering accomplishment not only allowed the commercial production of PGs of great therapeutic value but also contributed enormously to the progress of fundamental life science.

Now this field is shifting to a new phase for which new PGs must be synthesized. Several ongoing projects that reflect these new directions are described below.

Synthesis of Isocarbacyclin

The three-component synthesis developed in our laboratories consists of a one-step construction of the PG framework by combining the C_8 and C_7 side chains with the cyclopentenone unit (Fig. 1). Various new selective reagents containing main-group and transition metal elements as well as asymmetric reactions (*3*) were essential in realizing the long-sought synthesis (*4*, *5*). Use of a C_8 organometallic reagent and a C_7 acetylenic halide as the lower and upper side-chain units, respectively, leads to the 5,6-didehydro-PGE_2 derivative **1**, which serves as the common intermediate for the synthesis of most natural PGs. This direct method also allows preparation of a wide array of artificial analogs. Particularly significant is the synthesis of isocarbacyclin (**2**), a promising therapeutic agent for various thrombotic diseases (*6*). Combination of a controlled radical reaction, photochemical process, and organometallic and organosilicon chemistry allowed the selective synthesis of **2** from the acetylenic intermediate **1** or related compounds (*7*). Although natural prostacyclin (PGI_2) (**3**) possesses remarkable physiological activities including antihypertensive and platelet-aggregation inhibiting effects, the high sensitivity of the 2-alkylidenetetrahydrofuran structure to hydrolysis has prevented its use as a therapeutic agent. The carbocyclic analog **2** overcomes this stability problem yet maintains sufficient physiological activities. A clinical trial is now in progress for the use of this compound in the treatment of cerebral ischemic disease and of peripheral vascular diseases.

A Probe for PG Receptors

PGI_2 activates adenylate cyclase in platelets, vascular smooth muscle, NCB-20 cells, and mastocytoma P-815 cells, but its low stability, the low concentration of a receptor in the cell membranes, and the lack of a suitable agonist or antagonist to facilitate purification of a receptor protein have prevented a

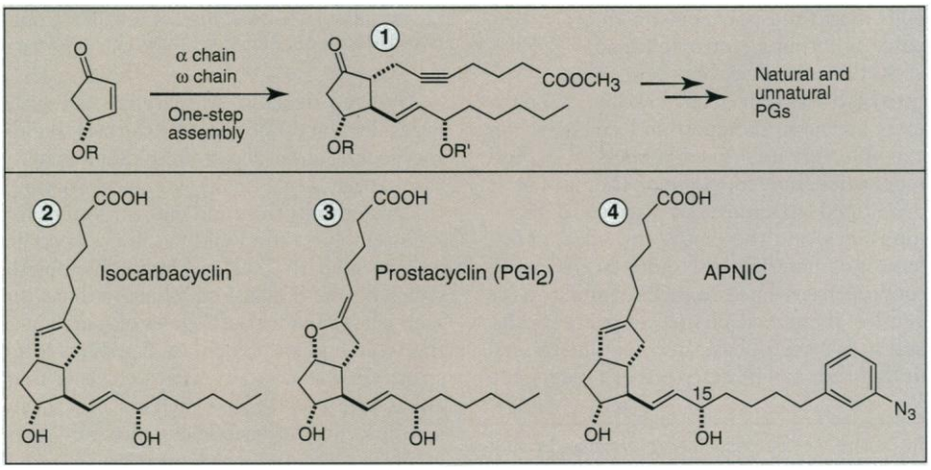

Fig. 1. Three-component synthesis for prostacyclins.

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molecular-level investigation of the receptors (*1*). Therefore, designing and synthesizing a probe that has sufficient chemical stability and high receptor affinity are crucial. The success of the three-component PG chemical synthesis led to the development of an efficient photoaffinity probe of the PGI_2 receptor, 19-(3-azidophenyl)-20-norisocarbacyclin (APNIC) (**4**) (Fig. 1), by structural modification of **2** (*8*). APNIC exhibits a specific, high affinity for the PGI_2 receptor [a 50% inhibitory concentration (IC_{50}) of 3 nM] and also acts as a PGI_2 agonist. The potency of **4** for the activation of adenylate cyclase was found to be 70% of that of iloprost, a commercial PGI_2 analog, and its rabbit platelet aggregation-inhibiting activity was one-fifth that of **2**. The photoaffinity labeling experiment with [15-^{3}H] APNIC as the ligand allowed for the first time the identification of PGI_2 receptor proteins of approximately 43 kD (mastocytoma P-815 cell), 45 kD (porcine platelet) (*9*), and 52 kD (human platelet) (*10*).

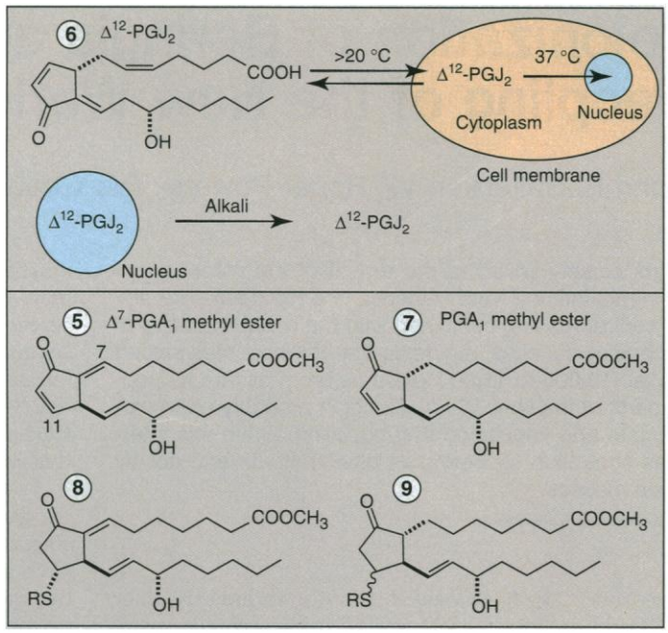

Fig. 2. Anticancer and antiviral prostaglandins.

Therapeutic PGs

PGs of the A and J series regulate cell cycles and participate in cellular defense against viral infection (*11*). Such PGs, which cause cell cycle arrest at the G_1 phase and inhibition of viral replication at noncytotoxic doses, may provide new therapeutic strategies. Some PG derivatives indeed show potent antitumor effects in vivo as well as in vitro without affecting adenosine 3',5'-monophosphate (cyclic AMP) concentrations (*12*). Particularly, Δ^7-PGA_1 methyl ester (**5**) (Fig. 2), a dienone easily made by the three-component synthesis by using a C_7 aldehyde as the upper side-chain unit (*5*), is now under preclinical study for the treatment of chemotherapeutically resistant ovarian cancer.

In L1210 murine leukemia cells, such PGs are controlled by a unique mechanism for cellular uptake and nuclear accumulation (*13*, *14*) illustrated in Fig. 2: (i) incorporation of PGs like Δ^{12}-PGJ_2 (**6**) into the cells is very rapid but reversible; an influx-efflux equilibrium is established at temperatures above 20°C; (ii) the considerable medium to cell concentration gradient favors cellular uptake; (iii) the intracellular PGs are incorporated into nuclei at 37°C without catabolism; and (iv) they are eventually bound to nuclear proteins. This binding is covalent and irreversible under physiological conditions; only alkali treatment can break the bond to regenerate the PGs. The structure-activity relation indicates that a cross-conjugated cyclopenatadienone system is essential for potent antitumor activity (*12*); 2-cyclopentenone or 2-alkylidenecyclopentanone derivatives are much less effective. Indeed, unconventional PGs like **5** and **6** (the ultimate active species from PGJ_2) are ideal compounds as antitumor agents. PGA_2, a simple enone analog, acts similarly but is bound to nuclei to a lesser extent. The facile synthesis of polyunsaturated PGs (*5*) prompted us to examine the chemical behavior of the dienone **5** and PGA_1 methyl ester (**7**), a cyclopentenone, under conditions that mimic the physiological situation in the cell. The dienone **5** in aqueous methanol (phosphate buffer, pH 7.4) was found to react with thiols such as methanethiol, mercaptoethanol, mercaptoacetic acid, cysteine, and glutathione, forming the Michael adducts of type **8**. The reaction occurs selectively at the C_{11} position, and the adducts have an 11,12-*trans* stereochemistry. The C_7 position of **8**, but not **5**, is susceptible to excess thiols, and 7,11-bis-thiol adducts are formed. The dienone, however, is inert to other biomolecules such as nucleotides, carbohydrates (glucose and 2'-deoxyglucose), or amino acids. The enone **7** behaves similarly to form the thiol adducts **9** (mixtures of epimers at C_{11}). The Michael addition of mercaptoethanol to the dienone **5** at 25°C occurs six times faster than the reaction to the enone **7**. Notably, this process is reversible and the dienone-thiol adduct is substantially less stable than the enone-thiol adduct [the dissociation constant (K_d) for **8** is 3.3 mM in contrast to 0.11 mM for **9**]. The glutathione-PG adducts behave similarly: the K_d for **8** is 2.9 mM, and for **9**, 0.16 mM. In addition, the dienone **5** (methanol, pH 7.4, 25°C) is three times more reactive than the enone **7** toward Sepharose-bound mercaptoethanol or glutathione. The resulting polymer-anchored Michael adducts of type **8** and **9** are stable at pH 7.4 but release the thiols gradually above pH 9.5. Such kinetic and thermodynamic properties displayed by **5** and **7** are qualitatively consistent with the pharmacokinetics seen with radioactive **6** and PGA_2 under biological conditions. In cells, the dienones would react easily with small, soluble thiols such as cysteine or glutathione in a reversible fashion. The chemistry of these compounds suggests that, in the cytoplasm of L1210 cells, which contain 0.6 mM glutathione and 0.2 mM PG [maximum intracellular concentration attained by incubation of 0.01 mM PG at 37°C (*13*)], 83% of dienone **5** or 27% of enone **7** would exist in a free state and the remaining as the Michael adducts **8** and **9**, respectively. This equilibration facilitates influx and efflux of the PGs through cellular membranes and also allows transport to the nuclei. The covalently bound thiol adducts in nuclei in turn remain stable because of the decreased molecular motion in the polymeric biomatrices; the accumulated PGs are dissociated only by alkali treatment. The biological action of these compounds may be similar in viruses.

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15. We thank H. Koyano, M. Mori, R. Hirata, and T. Kokura for skillfully performing the experiments and M. Fukushima, S. Ito, and S. Kurozumi for their valuable comments and careful reviewing of the manuscript.