FTIR Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Agonist (U-46619), Prostaglandin (PG)E_2, PGD_2, $PGF_{2\alpha}$, Prostacyclin Receptor Agonist (Carbacyclin), and Their Related Compounds in Dilute CCl_4 Solution: Structure–Activity Relationships

Mamoru Takasuka,* Morio Kishi, and Masumi Yamakawa

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Received June 14, 1993•

FTIR spectra measurements and full optimization curve analysis of their spectra were done to obtain parameters of the OH and C=O stretching vibration bands for intramolecular hydrogen bondings in thromboxane (TX)A_2 receptor partial agonist (CTA_2), prostaglandin (PG)E_2, PGD_2, $PGF_{2\alpha}$, prostacyclin (PGI_2) receptor agonist (carbacyclin), and their related compounds in dilute CCl_4 solutions. For CTA_2, PGE_2, PGD_2, and $PGF_{2\alpha}$, cyclic intramolecular hydrogen bonds involving a 15-membered ring similar to that observed for the TXA_2 receptor agonist (U-46619) were found between a carboxyl group of the α-side chain and a 15-hydroxyl group of the ω-side chain. The arrangement of these side chains was P-shaped, and the percentage of the intramolecular hydrogen-bonded molecules with the 15-membered ring in CCl_4 solution showed a high value of ca. 80% for these compounds. In addition, it was found that the cyclic intramolecular hydrogen bonds involving the 13-, 12-, and 12-membered rings in PGE_2, PGD_2, and $PGF_{2\alpha}$, respectively, are formed between the carboxyl group of the α-side chain and the 11-, 9-, and 9-hydroxyl groups of a cyclopentane ring, respectively, although the percentages of the intramolecular hydrogen-bonded molecules with these membered rings are very small. It was also found that the hydrogen bond is more easily formed in the order of the 11-, 9-, and 15-hydroxyl groups. For carbacyclin, the cyclic intramolecular hydrogen bond involving the 13-membered ring was found between the carboxyl group of the α-side chain and the 11-hydroxyl group. The percentage of the intramolecular hydrogen-bonded molecules showed the value of 58% for carbacyclin. On the basis of information on the side-chain conformations in CCl_4, we examined the structure–activity relationships for U-46619 in place of TXA_2, PGE_2, PGD_2, $PGF_{2\alpha}$, and carbacyclin in place of PGI_2.

Introduction

Thromboxane (TX)A_2,[1] prostaglandin (PG)E_2,[2] PGD_2,[3] $PGF_{2\alpha}$,[4] and prostacyclin (PGI_2),[5] which possess various physiological activities at very low levels, can be biosynthesized from arachidonic acid through cyclooxygenase reaction (Figure 1).[6] Study of the physiological and pathophysiological roles and the effects of these physiological active compounds within the body should contribute to the development of new drugs.[7] Despite the similarity of the side chains of these compounds, they possess different physiological and pharmacological effects.[6,7] Therefore, we are interested in studying their structure–activity relationships.

The molecular structures of TXA_2, PGE_2, PGD_2, $PGF_{2\alpha}$, and PGI_2 binding to the receptors must be known in order to elucidate these relationships, but this has not been possible by X-ray crystallographic analysis. Hence their putative active conformations were estimated by the following methods. The crystal structures of PGE_2, $PGF_{2\alpha}$, PGB_1, the hydrolysis product (TXB_2) of TXA_2, and other prostaglandins were determined by X-ray crystallographic analysis.[8] The arrangements of the α- and ω-side chains in these compounds, except for PGB_1 which is an L-shaped structure[8f] and TXB_2 which has a scorpion structure,[9] showed a hairpin-like (U) structure in the crystal form.[8] However, these arrangements are not necessarily the same as the active conformations due to intermolecular hydrogen bonding and packing forces in the crystal. CD spectral study indicates that the shape of PGE_2 in solution is a U

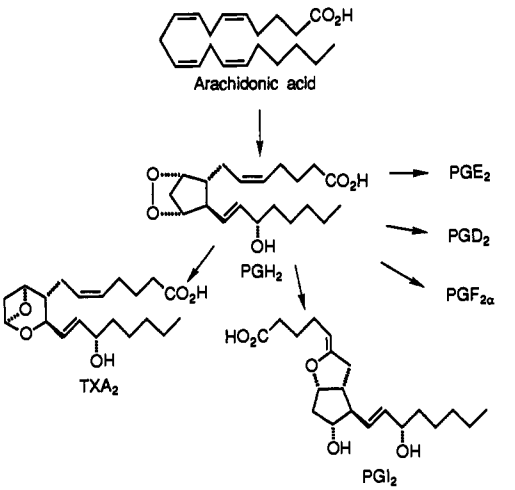


Figure 1. Principal products of cyclooxygenase.

structure, but this method cannot delineate detailed conformations beyond the 4-C and 16-C atoms of the side chains.[10] The solutions of various prostaglandins were examined by the ^1H NMR (NOE difference) spectral method, though this method cannot provide detailed active conformations because of rapid interconversion, by rotation about C–C single bonds of the side chains, although the shape of these prostaglandins was indicated to be of the U structure.[11]

In addition, conformational analyses on TXA_2 and PGI_2, which are unstable compounds, were carried out by molecular mechanics and molecular orbital methods, and their active conformations were estimated to be the U and

• Abstract published in *Advance ACS Abstracts*, November 15, 1993.

0022-2623/94/1837-0047$04.50/0

elongated structures, respectively.[12,13] However, these conformations were determined without consideration of the environment of the binding site in the receptors, which is particularly important for assessing the structure–activity relationship of TXA_2, PGE_2, PGD_2, $PGF_{2\alpha}$, and PGI_2 containing the α- and ω-side chains. No study of systematical conformational analysis with this consideration has been reported on the active conformations of these compounds. The conformations have been determined by various methods, but detailed information has not yet been obtained.

In calculating the electrostatic interaction in proteins, a dielectric constant (d) suitable for their interiors was assumed to be in the range 2–5 or to be 3.5.[14,15] This constant was theoretically estimated to be ca. 2.5.[16] If a hole is considered to exist in a protein as the binding site in the receptors, the d value of this site is presumed to be not more than these d values. The nonpolar hydrocarbon phase where the d value is ca. 2 has been reported to be suitable as the environment for the binding site.[17] The d value of CCl_4 is 2.228 at 25 °C. Therefore, we expect that information can be obtained for the active conformation of the above compounds when their FTIR spectra are measured in dilute CCl_4 solution. However, no information is avilable on the conformation in cyclooxygenase-derived eicosanoids and their related compounds, except for the compounds we report below.

Recently, we measured the FTIR spectra of TXA_2 receptor agonist, U-46619,[18] and its antagonists, S-145,[19] and five other compounds, in dilute CCl_4 solution, carried out full optimization curve analysis of their spectra, and found that the intramolecular hydrogen bonds involving a large-membered ring of more than 11 in these compounds are formed between the carboxyl group of the α-side chain and a functional group of the ω-side chain.[20,21] On the basis of this finding, the conformations of the side chains in these compounds were found to be similar to each other and to be of a P-shaped structure rather than the U-shaped one in dilute CCl_4 solution. The active conformation of these compounds was anticipated to differ from the intramolecular hydrogen-bonded one because the carboxyl group appears to be of importance in the exhibition of the TXA_2 receptor agonistic or antagonistic activity. However, these compounds mainly existed in the larger-membered ring in dilute CCl_4 solution, where the environment is presumed to be similar to that of the binding site in the TXA_2 receptor as mentioned above. Therefore, it was assumed that even if the active conformations are of the nonintramolecular hydrogen-bonded one type, they would not greatly differ from the conformation of the large-membered ring. On the basis of this assumption, we investigated the structure–activity relationships for S-145 and its analogues and found that the structure easily derived from the 12-membered one formed by the intramolecular hydrogen bonds plays an important role in the appearance of the TXA_2 receptor antagonistic activities.[22]

Thus, in order to determine the conformation of the side chains in the title compounds, we synthesized compounds **2-6**, **8**, and **9** and measured the FTIR spectra of 11a,21-dicarba-TXA_2 (CTA_2) and **1-10** (Figure 2) and 9-deoxo-9-methylene-PGE_2 (**11**) in dilute CCl_4 solutions. A bicyclic ring of CTA_2 is similar to that of TXA_2, although CTA_2 is a TXA_2 receptor partial agonist.[23] On the basis of the results obtained, we examined the structure–activity relationships for TXA_2, PGE_2 (**1**), PGD_2 (**3**), $PGF_{2\alpha}$ (**7**),

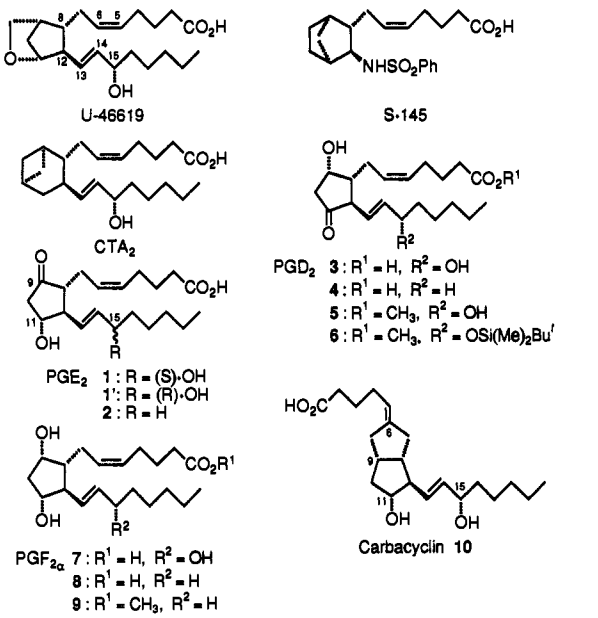


Figure 2. TXA_2 receptor agonist, U-46619, its antagonist, S-145, and its partial agonist, CTA_2, and PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 receptor agonist, carbacyclin, and their related compounds.

and PGI_2, where TXA_2 and PGI_2 were substituted by U-46619 and carbacyclin (**10**),[24] respectively, because they are unstable. Since the percentages of the large-membered ring linked by the intramolecular hydrogen bonds in U-46619, S-145, and their related compounds increase with a decreasing d value of the solvent,[20,21] the information obtained by the FTIR method should be useful for evaluating the conformational analyses using theoretical calculations which are usually carried out under vacuum (d = 1).

Experimental Section

Compound **1** was obtained commercially from Nacalai Tesque, Ltd., **7** from Chinoin Pharmaceutical and Chemical Works, Ltd., and CTA_2, **1'**, and **11** from Cayman Chemical Co. Compounds **3**, **5**, and **6** were prepared according to the modified method of the literature procedure.[25a,b] Compounds **2**, **4**, **8**, and **9** were synthesized by us[25c] and **10** at our laboratory.[24] The FTIR spectra were recorded on a Nicolet 20 SXB FTIR spectrometer at ca. 27 °C. The solvent CCl_4 was dried over 4-Å molecular sieves and purified by distillation. All compounds were dissolved in CCl_4 at concentrations (c) below 4×10^{-5} M (cell length = 5.0 cm). FTIR spectra of methyl esters **5**, **6**, and **9** were also measured in CCl_4 at ca. 5×10^{-4} M (cell length = 2.0 cm). All operations for these solutions were performed in a dry box filled with N_2 gas. The full optimization curve analysis for peak separation of the spectra observed was carried out using the Nicolet FOCAS program. This calculation allows the parameters of band frequency, band width at half-intensity, absorbance, and composition as the percent Gaussian vs Lorentzian contribution to each individual curve.

It was assumed that the values of the molecular coefficients (ϵ/mol^{-1} dm^3 cm^{-1}) of the free carbonyl stretching vibration bands (free $\nu_{C=O}$ bands) for the carboxyl group in CTA_2, **1-4**, **7**, **8**, **10**, and **11** and for a carbomethoxy group in **5**, **6**, and **9** are equal to the ϵ value of the band at 1759 cm^{-1} in lauric acid and to the ϵ value of the band at 1742 cm^{-1} in methyl stearate, respectively.[20] The percentages (N) of non-hydrogen-bonded molecules for these compounds were estimated using these ϵ values because they are larger than those of the free ν_{OH} bands at 3533 cm^{-1} for the carboxyl group in lauric acid and at ca. 3620 cm^{-1} for the hydroxyl group in alcohols. These N values were reproduced within ±2% for several measurements.

Results and Discussion

The spectral data obtained for dilute CCl_4 solutions of CTA_2 and **1-11** at c below 4×10^{-5} M are listed in Table

Table I. FTIR Spectral Data[a] of CTA_2 and 1-11 in CCl_4

compd	assign.[b]	ν_{OH} or $\nu_{C=O}$/cm^{-1}	ϵ/mol^{-1} dm^3 cm^{-1}	$\Delta\nu_{1/2}$/ cm^{-1}	10^8A/cm^2 s^{-1} molecule^{-1}	N[c]/%	σ[d]/%	ρ[e]/%	10^5c/M
CTA_2	CO_2H, F	1758.3	136.0	17.1	28.7	27.1	0.5	72.4	2.5536
	H	1733.8	314.1	20.3	84.7				
	H	1717.4	70.5	24.2	22.9				
1	CO_2H, F	1758.7	89.0	20.1	22.3	17.7	0.1	82.2	2.8540
	H	1735.6	204.6	16.8	42.0				
	H	1714.1	188.9	29.4	69.2				
	9-C=O, F	1748.4	618.1	11.9	102.1				
1′	CO_2H, F	1757.4	77.1	17.3	16.4	15.4	0	84.6	2.5307
	H	1734.6	272.1	14.8	49.4				
	H	1719.1	173.9	30.0	67.6				
	9-C=O, F	1748.7	611.9	11.9	101.3				
2	CO_2H, F	1759.4	409.4	17.0	87.8	81.6	10.5	7.9	2.9900
	H	1737.3	118.6	17.2	26.5				
	H[g]	1711.1	101.1	16.4	20.4				
	9-C=O, F	1748.6	614.2	12.0	95.8				
3	CO_2H, F	1758.1	49.1	20.1	12.4	9.8	0	90.2	2.9733
	H	1737.4	314.7	20.5	82.8				
	H	1722.7	120.3	33.4	49.0				
	11-C=O, F	1748.8	589.2	10.8	90.1				
4	CO_2H, F	1758.5	324.4	18.8	77.0	64.6	6.4	29.0	2.9424
	H	1734.7	133.0	18.9	33.0				
	H[g]	1711.1	117.3	18.9	27.1				
	11-C=O, F	1747.5	560.0	12.4	87.2				
5[h]	9-OH, F	3625.0	84.5	17.5	20.8	(86.8)	*i*	13.2	2.9359
	15-OH,[j] F	3611.2	51.3	25.1	15.8			(32.3)	
	OH, H	3538.6	69.9	76.4	68.5		*i*		
	CO_2CH_3, F	1742.0	299.9	14.1	51.6	54.5		45.5	
	H	1726.8	321.0	15.9	69.2				
	11-C=O, F	1748.9	548.5	12.4	95.7				
6[h]	9-OH, F	3626.4	60.8	15.4	12.2				3.0451
	H	3547.3	58.3	75.4	54.8				
	CO_2CH_3, F	1742.6	343.6	14.3	60.2	62.5	*i*	37.5	
	H	1726.7	274.1	16.2	60.2				
	11-C=O, F	1749.1	529.2	12.4	92.2				
7	CO_2H, F	1756.1	87.0	20.4	21.7	17.3	0	82.7	(2.2070)[h]
	H	1734.4	344.8	19.2	86.7				
	H	1713.1	94.5	21.8	25.6				
8	CO_2H, F	1757.7	295.5	20.4	74.4	58.9	5.3	35.8	2.9543
	H	1737.8	85.6	23.4	26.4				
	H[g]	1710.5	128.3	19.1	30.5				
9[h]	OH,[j] F	3615.4	56.1	29.8	20.4				2.9333
	H	3547.0	69.9	72.3	63.3				
	CO_2CH_3, F	1741.8	404.0	16.1	88.8	73.5	*i*	26.5	
	H	1726.8	141.0	17.5	30.5				
10	CO_2H, F	1757.9	198.1	18.5	49.0	39.5	2.2	58.3	3.0585
	H	1737.1	81.9	25.9	25.9				
	H[g]	1711.0	167.7	24.1	53.8				
11[m]	CO_2H, F	1757.8	82.0	18.6	18.7	16.3	0.2	83.4	3.8174
	H	1733.5	184.3	22.2	50.9				
	H	1710.2	179.2	21.3	56.6				

[a] ν, ϵ, $\Delta\nu_{1/2}$, and A are the band frequency, the molar absorption coefficient, the band width at half-intensity, and the integrated intensity, respectively. [b] F and H show free and intramolecular hydrogen-bonded ν_{OH} or $\nu_{C=O}$ bands, respectively. [c] Percentage (N) of non-hydrogen-bonded molecules, $N = (\epsilon/501.9)100$ or $N = (\epsilon/550.0)100$, where 501.9 is the ϵ value of 100% free $\nu_{C=O}$ band of lauric acid and 550.0 is the ϵ value of free $\nu_{C=O}$ band of methyl stearate.[20] However, the N value of 1 and 3 was estimated using the ϵ value of the free ν_{OH} band of the carboxyl group and the equation [$N = (\epsilon/178.4)100$] because the band was weak and was overlapped by the $\nu_{C=O}$ band of the carbonyl group, where 178.4 is the ϵ value of 100% free ν_{OH} band of lauric acid.[20] The N value in parentheses is the percentage of molecules with the free 9-hydroxyl group and was estimated using the equation, $N = (\epsilon/97.3)100$, where 97.3 is the ϵ value of 100% free ν_{OH} band of **6**. [d] Percentage (σ) of dimers: the value was approximately estimated using the equations,[21] $\log c_f = 0.245\sigma_0^{1/2} - 5.492$ and $\sigma = \sigma_0 N/100$, where c_f is the concentration of free molecules ($c_f = cN/100$) and σ_0 is the percentage of dimers at c_f. [e] Percentage (ρ) of intramolecular hydrogen-bonded molecules, $\rho = 100 - (N + \sigma)$. The ρ value in parentheses is the percentage of molecules which form the hydrogen bond between the 15-hydroxyl and carbomethoxy groups and was the difference between the total ρ value (45.5) and 13.2, where 13.2 is the percentage of molecules which form the hydrogen bond between the 9-hydroxyl and carbomethoxy groups.[35] [f] Concentration. [g] The band may be overlapped by the dimer $\nu_{C=O}$ band at ca. 1711 cm^{-1}.[20] In **2**, the greater part of the band is the dimer $\nu_{C=O}$ band. [h] The FTIR spectral data agreed very closely with those at ca. 5×10^{-4} M. [i] The compound does not form the dimers: $\sigma = 0$. [j] The band was assigned to the 15-hydroxyl group because the ν_{OH} band of 1-octen-3-ol was not observed at wavenumbers higher than 3620 cm^{-1}.[20] This group may be intramolecular hydrogen-bonded to the C_{13}=C_{14} double bond. [k] The average of total A values of the $\nu_{C=O}$ bands for the carboxyl group observed for CTA_2, 1-4, 8, 10, and 11 was 134×10^{-8} cm^2 s^{-1} molecule^{-1}. The c value of **7** was estimated from this value because the compound could not be completely dissolved in CCl_4. [l] The bands at 3615 and 3547 cm^{-1} were assigned to the free ν_{OH} and intramolecular hydrogen-bonded ν_{OH} bands because they agreed with these bands at 3619 and 3544 cm^{-1} of *cis*-cyclopentane-1,3-diol, respectively.[37] The latter band at 3547 cm^{-1} is overlapped by the intramolecular hydrogen-bonded ν_{OH} bands formed between the hydroxyl and carbomethoxy groups as in (C). [m] 9-Deoxo-9-methylene-PGE_2.

I together with the assignments of peaks and the N, σ, and ρ values, where σ is the percentage of dimers formed by intermolecular hydrogen bonds between the carboxyl groups and ρ (=100 − N − σ) is the percentage of the intramolecular hydrogen-bonded molecules. These compounds in these solutions do not form the intermolecular hydrogen bonds between the functional groups, except for the dimers.[20,21] Although there is little possibility of dimerization due to the formation of the intramolecular hydrogen bonds, the σ values of these compounds were

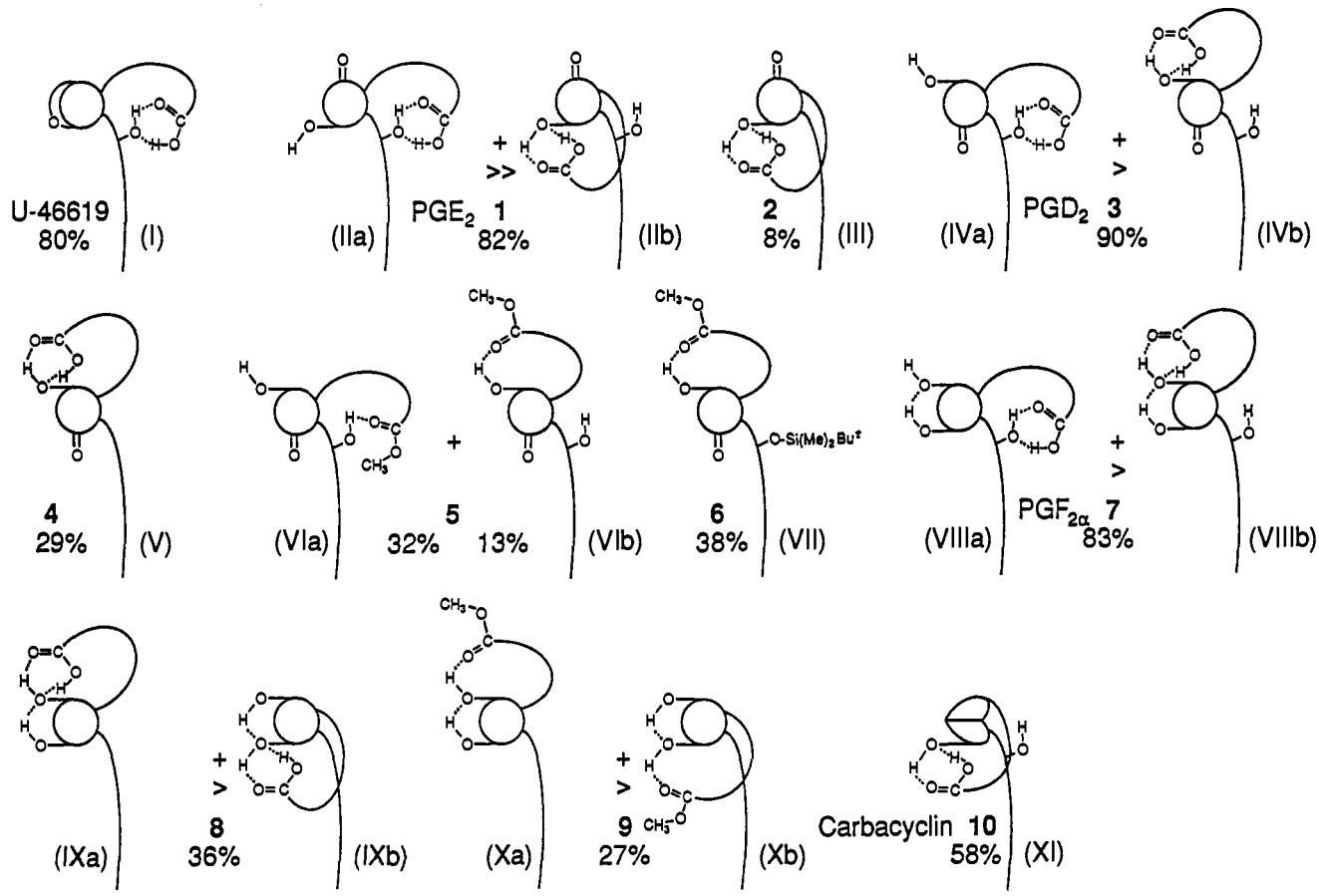
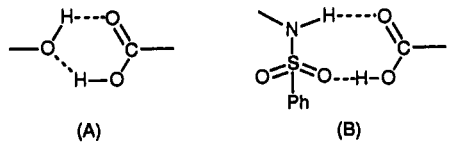


Figure 3. The schematic diagrams of structures and the ρ values of the intramolecular hydrogen-bonded molecules in U-46619[20] and 1-10 in CCl_4. The structure as in the (III) type in 7 was omitted because the ρ value was presumed to be far smaller than that of the structure (VIIIb) (see text).

estimated by the method shown in Table I, footnote *d*. From the structural standpoint, these compounds cannot form the intramolecular hydrogen bonds between the 15-hydroxyl group and the 9- or 11-carbonyl and hydroxyl groups, but they may form a negligibly weak one between the 9- or 11-hydroxyl group and the π-electrons on the 11- or 9-carbonyl group, although its hydrogen bond is not discussed here. In general, the formation of the hydrogen bonds, XH···O=Y and XH···Z, causes a shift of the stretching vibration bands, ν_{XH} and $\nu_{Y=O}$ bands, to lower wavenumbers.[26-28] The schematic diagrams I-XI of structures of the intramolecular hydrogen-bonded molecules found for U-46619[20] and 1-10 and the ρ values are shown in Figure 3.

TXA_2 Receptor Agonist, U-46619, Its Antagonist, S-145, and Its Partial Agonist, CTA_2. U-46619 and S-145 in dilute CCl_4 solution mainly exist in conformations with the 15-membered ring (I) and the 12-membered one formed by the cyclic intramolecular hydrogen bonds (A and B) between the functional groups of the α- and ω-side chains, respectively.[20] U-46619 gave two intramolecular



hydrogen-bonded $\nu_{C=O}$ bands at 1736 and 1721 cm^{-1}, indicating that an equilibrium exists between two conformers which are attributable to the C_5=C_6 double bond as observed for S-145 and its related compounds.[20-22,29] The spectral behavior of CTA_2 strongly resembles that of U-46619. This indicates that CTA_2 exists in conformations with the 15-membered ring due to the cyclic intramolecular hydrogen bond (A) between the carboxyl and hydroxyl groups as in U-46619. The ρ values of CTA_2 and U-46619 are estimated to be 72 and 80%, respectively. The difference between these values may be significant, because it is expected that CTA_2 with a bicyclo[3.1.1]heptane ring exists as a mixture of two conformers with diequatorial side chains and with diaxial ones which are unfavorably oriented for the cyclic intramolecular hydrogen bond (A) to be formed.[30] These ρ values are much larger than the 24% of 12-hydroxystearic acid which forms the 15-membered ring via the cyclic intramolecular hydrogen bond (A).[22] This is attributable to the degree of freedom in the motions of the α- and ω-side chain in U-46619 and CTA_2 being smaller than that of 12-hydroxystearic acid, which is a chain compound, because U-46619 and CTA_2 have rigid moieties, two double bonds and a bicyclic ring. As the degrees of freedom in the conformations of the 15-membered ring in U-46619 and CTA_2 are very small owing to those rigid moieties and the cyclic intramolecular hydrogen bond (A), it is presumed that there are few kinds of their ring conformers. On the other hand, PG-1,15-lactones have been found from a natural source, the nudibranch mollusc *Tethys fimbria*.[31] This suggests the cyclic intramolecular hydrogen bond (A) can be formed in organisms.

PGE_2 (1), 15-Epi-PGE_2 (1'), and 15-Deoxy-PGE_2 (2). As shown in Figure 4, compounds 1 and 2 exhibit four $\nu_{C=O}$ bands. For 1 and 2, the intensities of the free $\nu_{C=O}$ bands at 1759 cm^{-1} for the carboxyl groups decreased and two intramolecular hydrogen-bonded $\nu_{C=O}$ bands appeared

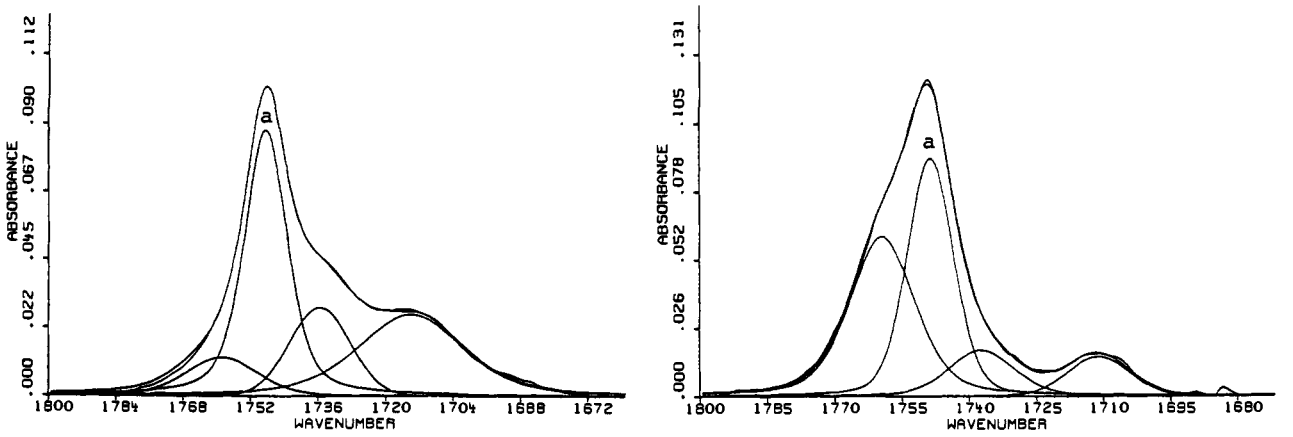


Figure 4. FTIR spectra of PGE_2 (1) (left) and 15-deoxy PGE_2 (2) (right) in CCl_4 and the results of peak separations of their spectra. Spectra were obtained with a 5.0-cm cell: 1, 2.8540×10^{-5} M and 2, 2.9900×10^{-5} M. a: The $\nu_{C=O}$ band for 9-carbonyl group.

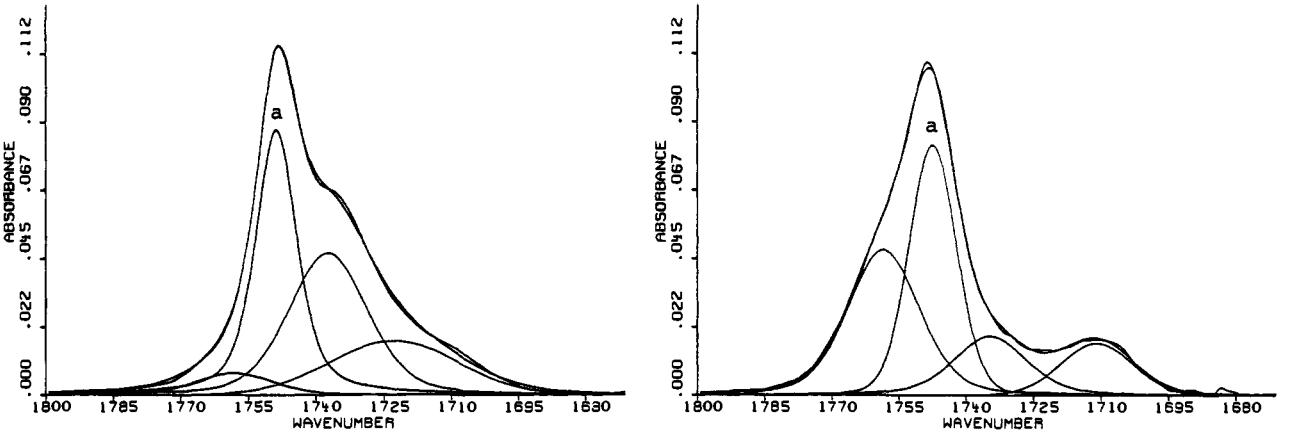


Figure 5. FTIR spectra of PGD_2 (3) (left) and 15-deoxy-PGD_2 (4) (right) in CCl_4 and the results of peak separations of their spectra. Spectra were obtained with a 5.0-cm cell: 3, 2.9733×10^{-5} M and 4, 2.9424×10^{-5} M. a: The $\nu_{C=O}$ band for 11-carbonyl group.

at 1736 and 1714 cm^{-1} and at 1737 and 1711 cm^{-1}, respectively. The spectral behaviors of 1′ strongly resemble those of 1. These spectral changes are much larger than those of 2. However, the intensities of the free $\nu_{C=O}$ band at ca. 1748 cm^{-1} for the 9-carbonyl group in 1 and 1′ are the same as that of 1749 cm^{-1} in 2. This indicates that the intramolecular hydrogen bond is scarcely formed between the 9-carbonyl and carboxyl groups. Furthermore, the intensities of the free ν_{OH} bands for the 15-hydroxy group[32] and for the carboxyl group at ca. 3530 cm^{-1} (ϵ = ca. 28) in 1 and 1′ markedly decreased and a broad band appeared at ca. 3200 cm^{-1}. For 2, the intensities of the free ν_{OH} bands for the 11-hydroxyl group[32] and for the carboxyl group at 3532 cm^{-1} (ϵ = 146) slightly decreased.[33]

From these findings, it is clear that the cyclic intramolecular hydrogen bonds (A) involving the 15-membered ring (IIa) in 1 and the 15-membered ring in 1′ are formed between the 15-hydroxyl and carboxyl groups as well as the 13-membered ring (III) in 2 between the 11-hydroxyl and carboxyl groups. These compounds gave the two hydrogen bonded $\nu_{C=O}$ bands, indicating that an equilibrium exists between two conformers due to the $C_5{=}C_6$ double bond. The ρ values of 1, 1′, and 2 are estimated to be 82, 85, and 8%, respectively. This indicates that the conformations of the 15-membered ring formed by the cyclic intramolecular hydrogen bonds (A) in 1 and 1′ are not appreciably influenced by the configuration of the 15-hydroxyl group although the direction of the ω-side chain in 1′ is shifted to the right by more than 60° compared with that in (IIa) of 1. The ρ value of 1 is much larger than that of 2 and is indistinguishable from that of U-46619 within the experimental error limit of 2%. These results also indicate that the formation of the 15-membered ring (IIa) in 1 occurs more easily than that of the 13-membered ring (III) in 2. However, it is presumed that 1 forms several percent of the 13-membered ring (IIb) similar to that of (III) because 1 has an additional 11-hydroxyl group.

PGD_2 (3) and 15-Deoxy-PGD_2 (4). As shown in Figure 5, compounds 3 and 4 also exhibit four $\nu_{C=O}$ bands. For 3 and 4, the intensities of the free $\nu_{C=O}$ bands at 1758 and 1759 cm^{-1} for the carboxyl groups decreased and two intramolecular hydrogen-bonded $\nu_{C=O}$ bands appeared at 1737 and 1723 cm^{-1} and at 1735 and 1711 cm^{-1}, respectively, indicating that an equilibrium exists between two conformers which are attributable to the $C_5{=}C_6$ double bond. These spectral changes of 3 are larger than those of 4. On the other hand, the intensity of the free $\nu_{C=O}$ band at 1749 cm^{-1} for the 11-carbonyl group in 3 is nearly equal to that of 1748 cm^{-1} in 4. This indicates that little formation of the intramolecular hydrogen bond occurs between the 11-carbonyl and carboxyl groups. In addition, the free ν_{OH} bands for the 15-hydroxyl group[34] and for the carboxyl group at ca. 3528 cm^{-1} (ϵ = ca. 18) in 3 almost disappeared and a broad band appeared at ca. 3150 cm^{-1}. For 4, the intensities of the free ν_{OH} bands at 3627 cm^{-1} for the 9-hydroxyl group[34] and at 3532 cm^{-1} (ϵ = 129) for the carboxyl group decreased.[33]

From these findings, it is evident that the intramolecular hydrogen bonds (A) involving the 15-membered ring (IVa) in 3 and the 12-membered ring (V) in 4 are formed between the 15-hydroxyl and carboxyl groups and between the 9-hydroxy and carboxyl groups, respectively. The ρ values of 3 and 4 are estimated to be 90 and 29%, respectively.

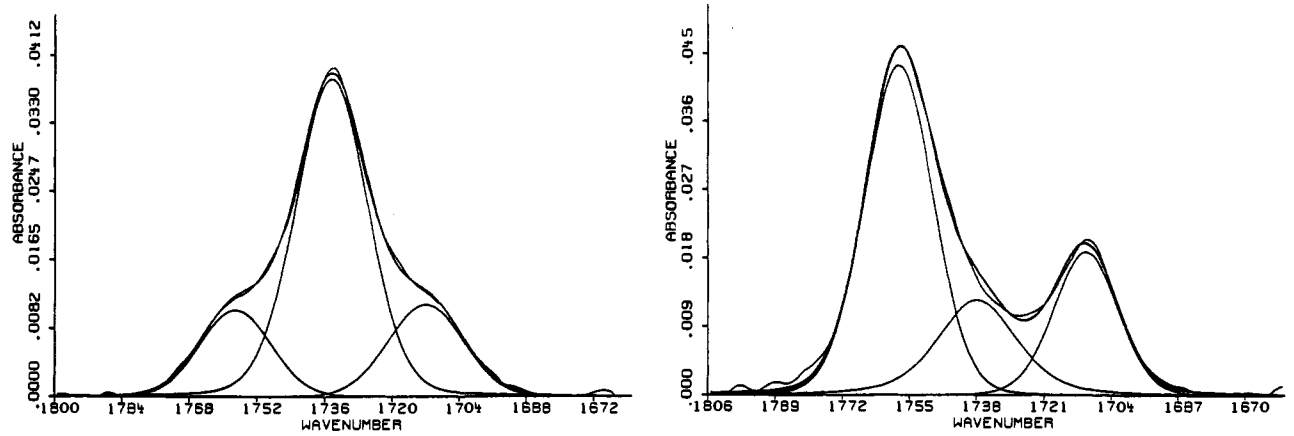
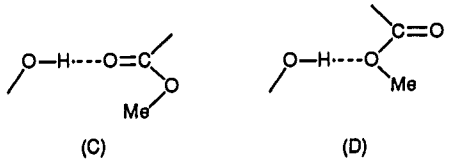


Figure 6. FTIR spectra of $PGF_{2\alpha}$ (7) (left) and 15-deoxy-$PGF_{2\alpha}$ (8) (right) in CCl_4 and the results of peak separations of their spectra. Spectra were obtained with a 5.0-cm cell: 7, (2.2070×10^{-5} M)[a] and 8, 2.9543×10^{-5} M.[a] See Table I, footnote *k*.

The former value is larger than that of U-46619, suggesting that **3** forms ca. 10% of the 12-membered ring (IVb) similar to (V) observed for **4** because **3** has an additional 9-hydroxyl group. The ρ value in compounds containing only one hydroxyl group becomes larger in the order of **2**, **4**, and U-46619. This indicates that the formation of the cyclic intramolecular hydrogen bond (A) occurs more easily in the order of the 11-, 9-, and 15-hydroxyl groups. Since this order does not agree with the increase in the size of the ring formed by the hydrogen bond (A), the ρ value in these compounds is primarily governed by steric factors.

PGD_2 Methyl Ester (5) and 15-$Bu^t(Me)_2SiO$-PGD_2 Methyl Ester (6). For **5** and **6**, three $\nu_{C=O}$ bands were observed at 1749, ca. 1742, and 1727 cm^{-1}, which were assigned to the free $\nu_{C=O}$ band of the 11-carbonyl group and the free and intramolecular hydrogen-bonded $\nu_{C=O}$ bands of the carbomethoxy group, respectively. Correspondingly, the intensities of the free ν_{OH} bands at 3625 cm^{-1} for the 9-hydroxyl group and at 3611 cm^{-1} for the 15-hydroxyl group in **5** and at 3626 cm^{-1} for the 9-hydroxyl group in **6** decreased[35] and the intramolecular hydrogen-bonded ν_{OH} bands of the former appeared at 3539 cm^{-1} and of the latter at 3547 cm^{-1}. These results indicate that intramolecular hydrogen bonds (C) involving the 15-membered ring (VIa) and the 12-membered one (VIb) in **5** and the 12-membered one (VII) in **6** are formed between the 15- or 9-hydroxyl and carbomethoxy groups and between the 9-hydroxyl and carbomethoxy groups, respectively, because the formation of the hydrogen bond (D) causes a shift of the $\nu_{C=O}$ band of the carbomethoxy group to higher wavenumber.[36]



The ρ values of (VIa) and (VIb) for **5** are estimated to be 32 and 13%, respectively. This indicates that the formation of the intramolecular hydrogen bond (C) occurs more easily in the 15-hydroxyl group than in the 9-one. This order is similar to that of the cyclic intramolecular hydrogen bond (A). In spite of only one hydrogen bond existing in **6**, its ρ value of 38% is larger than that of **4** with two hydrogen bonds. This may be attributable to steric hindrance between the α-side chain and the ω-side chain with a $Bu^t(Me)_2SiO$ group. The spectral data in Table I of **5**, **6**, and **9** with the carbomethoxy group are very close to those obtained in CCl_4 solution at ca. 5×10^{-4} M.

$PGF_{2\alpha}$ (7) and 15-Deoxy-$PGF_{2\alpha}$ (8). As shown in Figure 6, the intensities of the free $\nu_{C=O}$ bands at 1756 cm^{-1} for the carboxyl group in **7** and at 1758 cm^{-1} for the carboxyl group in **8** decreased and the intramolecular hydrogen-bonded $\nu_{C=O}$ bands appeared at 1734 and 1713 cm^{-1} and at 1738 and 1711 cm^{-1}, respectively, indicating that an equilibrium exists between two conformers due to the $C_5{=}C_6$ double bond. These spectral changes of **7** are larger than those of **8**. Correspondingly, the intensity of the free ν_{OH} band at ca. 3532 cm^{-1} (ϵ = ca. 29) for the carboxyl group in **7** markedly decreased and a broad band appeared at ca. 3170 cm^{-1}. For **8**, the intensity of the free ν_{OH} band at 3532 cm^{-1} (ϵ = 106) for the carboxyl group decreased.[33] For **7** and **8**, intramolecular hydrogen-bonded ν_{OH} bands were observed at ca. 3559 cm^{-1} (ϵ = ca. 56) and ca. 3540 cm^{-1} (ϵ = ca. 47), respectively, indicative of the intramolecular hydrogen bond between the 9- and 11-hydroxyl groups.[37] Because of this hydrogen bond,[38] the free ν_{OH} band of these hydroxyl groups cannot be assigned, although its ν_{OH} band was also observed at ca. 3619 cm^{-1} for **7** and ca. 3614 cm^{-1} for **8**.[39] However, these results suggest that **7** mainly exists in conformation with the 15-membered ring (VIIIa) formed by the cyclic intramolecular hydrogen bond (A) between the 15-hydroxyl and carboxyl groups because the formation of the hydrogen bond (A) becomes more difficult in the order of the 15-, 9-, and 11-hydroxyl groups as mentioned above. The ρ value of **7** is estimated to be 83% and is not distinguishable from that of U-46619 within the experimental error limit of ±2%. However, it is inferred from these findings that, in addition to (VIIIa), **7** forms a small amount of the 12-membered ring (VIIIb) as in (V) observed for **4**, but little of the 13-membered ring as in (III) seen with **2**, although **7** has the additional 9- and 11-hydroxyl groups.

On the other hand, **8** is presumed to form the 12-membered ring (IXa) and the 13-membered ring (IXb) because its ρ value (36%) is close to the sum of those of the corresponding rings (V) in **4** and (III) in **2**. The ρ value of the (IXa) would be larger than that of the (IXb).

15-Deoxy-$PGF_{2\alpha}$ Methyl Ester (9). For **9**, the intensities of the free ν_{OH} band at 3615 cm^{-1} for the 9- and/or 11-hydroxyl groups[39] and the free $\nu_{C=O}$ band at 1742 cm^{-1} for the carbomethoxy group decreased and new bands appeared at 3547 and 1727 cm^{-1}, respectively; the former new band was overlapped by the intramolecular hydrogen-bonded ν_{OH} band formed between the 9- and 11-hydroxy groups.[40] The ρ value of **9** is estimated to be 27%. From

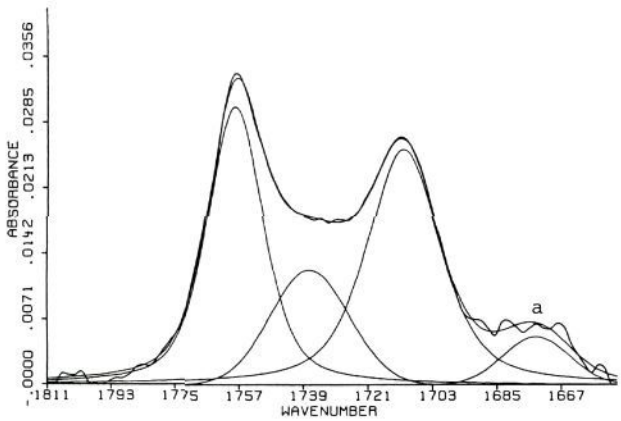


Figure 7. FTIR spectrum of carbacyclin (**10**) at 3.0585×10^{-5} M in CCl_4 in a 5.0-cm cell and the result of peak separation of the spectrum. a: The $\nu_{C=C}$ band for the $C_5{=}C_6$ double bond.

these results, it is also presumed that the intramolecular hydrogen bonds (C) involving the 12-membered ring (Xa) and the 13-membered ring (Xb) in **9** are formed between the 9-hydroxyl and carbomethoxy groups and between the 11-hydroxyl and carbomethoxy groups, respectively. The former ρ value would be larger than the latter one.

PGI_2 Receptor Agonist, Carbacyclin (10). As shown in Figure 7, the intensity of the free $\nu_{C=O}$ band at 1758 cm^{-1} for the carboxyl group in **10** decreased and two intramolecular hydrogen-bonded $\nu_{C=O}$ bands appeared at 1737 and 1711 cm^{-1}, indicating that the equilibrium exists between two conformers. Correspondingly, the intensities of the free ν_{OH} band for the 11-hydroxyl group[41] and for the carboxyl group at 3531 cm^{-1} ($\epsilon = 60$) in **10** decreased and a broad band appeared at ca. 3370 cm^{-1}. From the structural standpoint, this compound cannot form the intramolecular hydrogen bonds between the 11- and 15-hydroxyl groups and between the 15-hydroxyl and carboxyl groups. These results indicate that the cyclic intramolecular hydrogen bond (A) involving the 13-membered ring (XI) in **10** is formed between the 11-hydroxy and carboxyl groups. The ρ value of **10** is estimated to be 58%, which may be somewhat larger than that of PGI_2 because the 11-hydroxyl group of PGI_2 may form the intramolecular hydrogen bond with an oxygen atom of the 6,9-epoxy group.

Structure–Activity Relationships. As mentioned above, U-46619 and carbacyclin seem to possess only one structure with 15- and 13-membered rings, respectively, that differ remarkably from each other. On the other hand, PGE_2, PGD_2, and $PGF_{2\alpha}$ mainly exist as the 15-membered ring structure similar to that observed for U-46619 and have additional 13-, 12-, and 12-membered ring structures, respectively.

For all of these compounds, we consider that the interaction between the carboxyl group of the α-side chain and a functional group of the binding site in the receptors is essential for the exhibition of the biological or physiological activity. Therefore, it is assumed that the active conformation of these compounds is a nonintramolecular hydrogen-bonded one. However, these compounds exist in conformations with the large-membered rings in dilute CCl_4 solution, where the environment is presumed to be

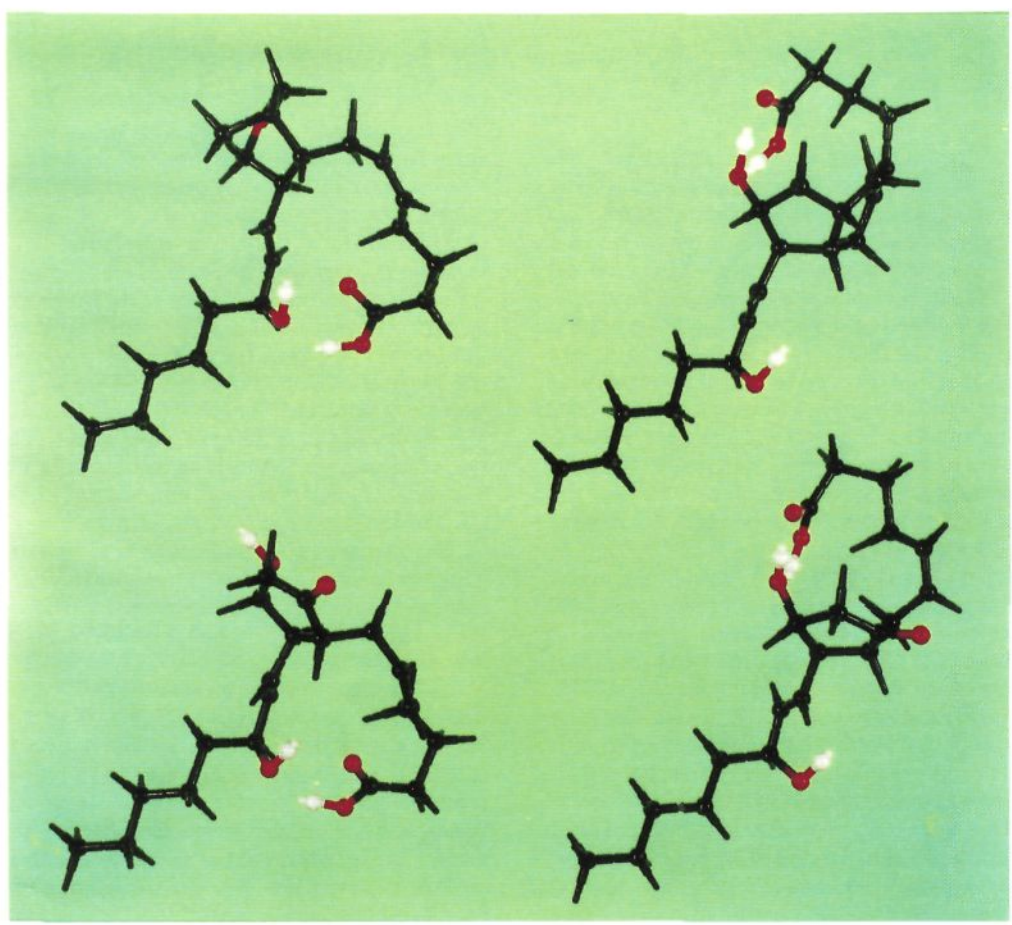


Figure 8. Molecular models of the intramolecular hydrogen-bonded structures (I) (upper left) of U-46619, (XI) (upper right) of carbacyclin, and (IIa) (lower left) and (IIb) (lower right) of PGE_2.

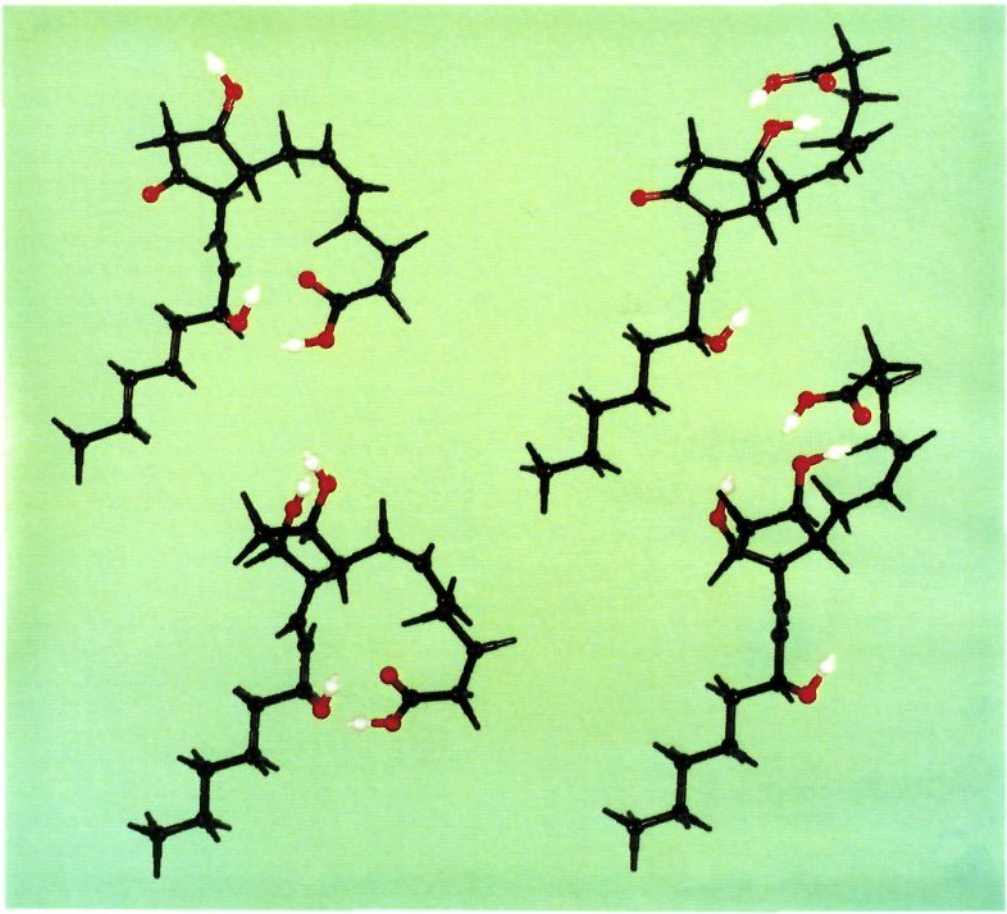


Figure 9. Molecular models of the intramolecular hydrogen-bonded structures (IVa) (upper left) and (IVb) (upper right) of PGD_2 and (VIIIa) (lower left) and (VIIIb) (lower right) of $PGF_{2\alpha}$.

similar to that of the binding site in the receptors as described in the Introduction. Thus it is supposed that even if the molecule cleaved is the active one, its conformation would be analogous to that of the large-membered ring formed by the cyclic intramolecular hydrogen bond (A) in dilute CCl_4 solution, where its hydrogen bond may play an important role in the formation of the conformation which is suitable for the binding site in the receptor. On the basis of this supposition, we investigated the structure–activity relationships with respect to vasoconstrictor and platelet aggregative actions *in vitro* of U-46619, PGE_2, PGD_2, $PGF_{2\alpha}$, and carbacyclin which were measured under the same condition, although other factors, besides the conformations formed by the hydrogen bond (A), may be important for receptor binding.

(1) In dog arteries, ONO-3708,[42] a receptor antagonist of TXA_2 which induces very potent vasoconstriction, selectively antagonizes not only the vasoconstrictor action of 11a-carba-21-thio-TXA_2[43] of which the two side chains and the configurations are the same as those of U-46619, but also that of PGE_2, PGD_2, and $PGF_{2\alpha}$, which share the same receptor site responsible for vascular contraction.[44] It has been also reported[45] that, in dog arteries, PGD_2 shares the mechanism underlying arterial contraction with PGE_2 and $PGF_{2\alpha}$. From these results, we inferred that the active conformations of U-46619, PGE_2, PGD_2, and $PGF_{2\alpha}$, which exhibit the vasoconstriction, have a common geometrical arrangement of the functional groups. We found that the conformation of the α- and ω-side chains in (I) of U-46619 is the same as those of (IIa) in PGE_2, (IVa) in PGD_2, and (VIIIa) in $PGF_{2\alpha}$ as shown in Figures 8 and 9. In addition, these compounds mainly existed in these conformations with the 15-membered ring in dilute CCl_4 solution. The results are consistent with the hypothesis mentioned above.

(2) PGE_2 and PGD_2 have been found not to bind at a low concentration to the platelet receptor of TXA_2 which induces very potent platelet aggregation, whereas PGE_2 binds to the platelet receptor of PGI_2 which shows a high inhibitory activity in the platelet aggregation and shows the low inhibitory activity, but PGD_2 does not.[46,47] It has been also reported[48] that PGD_2 binds to a receptor which differs from the PGI_2 receptor and inhibits platelet aggregation. We found that, as shown in Figures 8 and 9, only PGE_2 gives a small amount of the conformation (IIb) which is similar to the conformation (XI) of carbacyclin which is a PGI_2 receptor agonist. This finding agrees with the results reported above. Although PGE_1 also became bound to the platelet receptor of PGI_2,[47] its exact FTIR spectral data could not be obtained because of very low solubility in CCl_4.

PG activities has been reported to be markedly influenced by the configuration of the 15-hydroxyl group.[49] This can be attributed to the difference of compatibilities of the α- and ω-side chains for the binding site of PG receptors because the relative spatial arrangement between these chains is primarily governed by the cyclic intramolecular hydrogen bonds (A) as mentioned in 1 and 1′. The biological properties of 9-deoxo-9-methylene-PGs have been reported to be qualitatively very similar to those of the corresponding PGs.[50] Because the spectral behaviors of the carboxyl group (Table I) and of the hydroxyl groups[51]

in 9-deoxo-9-methylene-PGE_2 (11) are similar to those of PGE_2 (1), it is presumed that 11 mainly exists in the conformations of the (IIa) type similar to those of PGE_2. The ρ value of 11 was estimated to be 83%.[52] These results suggest that the α- and ω-side chains play an important role in the exhibition of the biological activities.

In conclusion, the FTIR method used should be useful for elucidating the conformation of analogous compounds containing nonvicinal carboxyl and other functional groups in CCl_4 solution. The information obtained should be helpful for predicting the structure of the binding site of receptor, for designing drugs, and for confirming the conformational analysis using theoretical calculations.

Acknowledgment. We thank Dr. H. Arita for his helpful discussions and Dr. S. Mori and Mr. H. Iwakura for providing carbacyclin. The cooperation of Mrs. M. Sugita is gratefully acknowledged.

References

(1) (a) Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: A New Group of Biologically Active Compounds Derived from Prostaglandin Endoperoxides. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994–2998. (b) Bhagwat, S. S.; Hamann, P. R.; Still, W. C. Synthesis of Thromboxane A_2. *J. Am. Chem. Soc.* **1985**, *107*, 6372–6376.

(2) Bergström, S.; Dressler, F.; Ryhage, R.; Samuelsson, B.; Sjövall, J. Prostaglandin and Related Factors. VIII. The Isolation of Two Further Prostaglandins from Sheep Prostate Glands. *Arkiv Kemi* **1962**, *19*, 563–567.

(3) (a) Granström, E.; Lands, W. E.; Samuelsson, B. Biosynthesis of 9α,15-Dihydroxy-11-ketoprost-13-enoic Acid. *J. Biol. Chem.* **1968**, *243*, 4104–4108. (b) Foss, P. S.; Sih, C. J.; Takeguchi, C.; Schnoes, H. Biosynthesis and Chemistry of 9α,15(*S*)-Dihydroxy-11-oxo-13-*trans*-prostenoic Acid. *Biochemistry* **1972**, *11*, 2271–2277.

(4) Bergström, S.; Dressler, F.; Krabisch, L.; Ryhage, R.; Sjövall, J. Isolation and Structure of a Smooth Muscle Stimulating Factor in Normal Sheep and Pig Lungs. *Arkiv Kemi* **1962**, *20*, 63–66.

(5) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. An Enzyme Isolated from Arteries Transforms Prostaglandin Endoperoxides to an Unstable Substance that Inhibits Platelet Aggregation. *Nature (London)* **1976**, *263*, 663–665.

(6) (a) Nicolaou, K. C.; Gasis, G. P.; Barnette, W. E. Synthesis and Biological Properties of Prostaglandin Endoperoxides, Thromboxanes and Prostacyclins. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293–378. (b) Samuelsson, B. Leukotrienes: Mediators of Immediate Hypersensitivity Reactions and Inflammation. *Science* **1983**, *220*, 568–575. (c) Prostaglandins and Related Substances; Benedetto, C.; McDonald-Gibson, R. G.; Nigam, S.; Slater, T. F., Eds.; IRL Press: England, 1987. (d) *Prostaglandins*; Bergström, S.; Samuelsson, B., Eds.; Almquist and Wiksell: Stockholm, 1966.

(7) (a) *CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids*; Willis, A. L., Ed.; CRC Press: Boca Raton, FL, 1987; Vol. I: Parts A and B; Vol. II. (b) *Prostaglandins, Leukotrienes, and Lipoxins: Biochemistry, Mechanism of Action, and Clinical Applications*; Bailey, J. M., Ed.; Plemum Press: New York, 1985. (c) *Drugs Affecting Leukotrienes and Other Eicosanoid Pathways*; Samuelsson, B., Berti, F., Folco, G. C., Velo, G. P., Eds.; Plenum Press: New York, 1985. (d) *The Ocular Effects of Prostaglandins and Other Eicosanoids*; Bito, L. Z., Stjernschantz, J., Eds.; Alan, R. Liss Inc.: New York, 1989. (e) *Prostaglandins in Cancer Research*; Garaci, E., Paoletti, R., Santoro, M. G., Eds.; Springer-Verlag: Berlin, Germany, 1987. (f) *Clinical Pharmacology of Prostacyclin*; Lewis, P. J.; Q'Grad, J., Eds.; Raven Press: New York, 1981.

(8) (a) DeTitta, G. T.; Langs, D. A.; Edmonds, J. W.; Duax, W. L. Prostadienoic Acids PGE_2 and $PGF_{2\beta}$: Crystallographic Studies of Conformational Transmission and Receptor Recognition. *Acta Crystallogr.* **1980**, *B36*, 638–645. (b) Langs, D. A.; Erman, M.; DeTitta, G. T. Conformations of Prostaglandin $F_{2\alpha}$ and Recognition of Prostaglandins by Their Receptors. *Science* **1977**, *197*, 1003–1005. (c) Fortier, S. F.; Erman, M. G.; Langs, D. A.; DeTitta, G. T. The Structure of Thromboxane B_2. *Acta Crystallogr.* **1980**, *B36*, 1099–1103. (d) Edmonds, J. W.; Duax, W. L. Crystal and Molecular Structure of the Orthorhombic Form of Prostaglandin A_1. *J. Am. Chem. Soc.* **1975**, *97*, 413–417. (e) Spek, A. L. The Crystal and Molecular Structure of Prostaglandin E_1. *Acta Crystallogr.* **1977**, *B33*, 816–824. (f) DeTitta, G. T. Prostaglandin B_1: The L-Shaped Prostaglandin. *Science* **1976**, *191*, 1271–1272. (g) Abrahamsson, S. A Direct Determination of the Molecular Structure of Prostaglandin $F_{2\alpha 1}$. *Acta Crystallogr.* **1963**, *16*, 409–418.

(9) Langs, D. A.; DeTitta, G. T.; Erman, M. G.; Fortier, S. Thromboxane Molecules are not Hairpin Conformers. *Adv. Prostaglandin Thromboxane Res.* **1980**, *6*, 477–480.

(10) Andersen, N. H.; Pamwell, P. W.; Leovey, E. M.; Johnson, M. Biological Consequences of Prostaglandin Molecular Conformations. *Adv. Prostaglandin Thromboxane Res.* **1976**, *1*, 271–289.

(11) Andersen, N. H.; Hartzell, C. J.; De, B. Chemistry and Structure of Cyclooxygenase-Derived Eicosanoids: A Historical Perspective. *Adv. Prostaglandin Thromboxane Res.* **1985**, *14*, 1–43 and other references cited therein.

(12) Ezumi, K.; Yamakawa, M.; Narisada, M. Computer-Aided Molecular Modeling of a Thromboxane Receptor Antagonist S-145 and Its Related Compounds. *J. Med. Chem.* **1990**, *33*, 1117–1122.

(13) Tsai, A.; Jager, E. V.; Wu, K. K. Conformation of Receptor-Associated PGI_2: An Investigation by Molecular Modeling. *J. Comput.-Aided Mol. Design* **1991**, *5*, 135–148.

(14) Gelin, B. R.; Karplus, M. Side-Chain Torsional Potentials: Effect of Dipeptide, Protein, and Solvent Environment. *Biochemistry* **1979**, *18*, 1256–1268.

(15) Rogers, N. K.; Sternberg, M. J. E. Electrostatic Interactions in Globular Proteins: Different Dielectric Models Applied to the Packing of α-Helices. *J. Mol. Biol.* **1984**, *174*, 527–542.

(16) Nakamura, H.; Sakamoto, T.; Wada, A. A Theoretical Study of the Dielectric Constant of Protein. *Protein Engineer* **1988**, *2*, 177–183.

(17) Wilkinson, A. J.; Warwick, C. M.; Davies, R. H. Electrostatic Interactions and Conformation of Some Thromboxane Antagonists. *Int. J. Quantum Chem. Quantum Biol. Symp.* **1988**, *15*, 67–84.

(18) (a) Bundy, G. L. The Synthesis Prostaglandin Endoperoxide Analogs. *Tetrahedron Lett.* **1975**, 1957–1960. (b) Di Minno, G.; Bertetti, V.; Bionchi, L.; Barbieri, B.; Cerletti, E.; Dejana, E.; Gaetano, G. D.; Silver, M. J. Effects of an Epoxymethano Stable Analog of Prostaglandin Endoperoxides (U-46619) on Human Platelets. *Thromb. Haemostasis* **1981**, *45*, 103–106.

(19) Narisada, M.; Ohtani, M.; Watanabe, F.; Uchida, K.; Arita, H.; Doteuchi, M.; Hanasaki, K.; Kakushi, H.; Otani, K.; Hara, S. Synthesis and in Vitro Activity of Various Derivatives of a Novel Thromboxane Receptor Antagonist, (±)-(5*Z*)-7-[3-*endo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic Acid. *J. Med. Chem.* **1988**, *31*, 1847–1854.

(20) Takasuka, M.; Yamakawa, M.; Watanabe, F. FTIR Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Antagonist S-145 and Related Compounds. Part 1. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1173–1179.

(21) Takasuka, M.; Yamakawa, M.; Ohtani, M. FTIR Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Antagonist S-145 and Related Compounds. Part 2. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1467–1479.

(22) Takasuka, M.; Yamakawa, M.; Ohtani, M. FTIR Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Antagonist S-145 and Related Compounds. 3. Conformation and Activity of S-145 Analogues. *J. Med. Chem.* **1991**, *34*, 1885–1891.

(23) (a) Ohuchida, S.; Hamanaka, N.; Hayashi, M. Synthesis of Thromboxane A_2 Analog, DL-(9,11),(11,12)-Dideoxa-(9,11),(11,-12)-dimethylene Thromboxane A_2. *Tetrahedron Lett.* **1979**, 3661–3664. (b) Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. Carbocyclic Thromboxane A_2. *J. Am. Chem. Soc.* **1980**, *102*, 1404–1409. (c) Lefer, A. M.; Smith, E. F., III; Araki, H.; Smith, J. B.; Aharony, D. A.; Claremon, D. A.; Magolda, R. L.; Nicolaou, K. C. Dissociation of Vasoconstrictor and Platelet Aggregatory Activities of Thromboxane by Carbocyclic Thromboxane A_2, a Stable Analog of Thromboxane A_2. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1706–1710.

(24) (a) Nicolaou, K. C.; Sipio, W. J.; Magolda, R. L.; Seitz, S.; Barnette, W. E. Total Synthesis of Carboprostacyclin, a Stable and Biologically Active Analogue of Prostacyclin (PGI_2). *J. Chem. Soc., Chem. Commun.* **1978**, 1067–1068. (b) Shibasaki, M.; Ueda, J.; Ikegami, S. New Synthetic Routes to 9(O)-Methanoprostacyclin. A Highly Stable and Biologically Potent Analog of Prostacyclin. *Tetrahedron Lett.* **1979**, 433–436.

(25) (a) Hart, T. W.; Metcalfe, D. A.; Sheinmann, F. Total Synthesis of (±)-Prostaglandin D_1: Use of Triethylsilyl Protecting Groups. *J. Chem. Soc., Chem. Commun.* **1979**, 156–157. (b) Nishizawa, E. E.; Miller, W. L.; Gorman, R. R.; Bundy, G. L.; Svensson, J.; Hamberg, M. Prostaglandin D_2 as a Potential Antithrombotic Agent. *Prostaglandins* **1975**, *9*, 109–121. (c) Kishi, M.; Takahashi, K.; Kawada, K.; Goh, Y. International Application No. PCT/JP 91/00305.

(26) (a) Flett, M. St. C. The Characteristic Infra-red Frequencies of the Carboxylic Acid Group. *J. Chem. Soc.* **1951**, 962–967. (b) Öki, M.; Iwamura, H.; Aihara, J. Intramolecular Interaction between Hydroxyl Group and Carbonyl Moiety in Keto-alcohols. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 176–182. (c) Joris, L.; Schleyer, P. R. Intramolecular Hydrogen Bonding in Aliphatic Hydroxy Ketones. *J. Am. Chem. Soc.* **1968**, *90*, 4599–4611. (d) Takasuka, M.; Matsui, Y.; Kubota, T. The Effect of Intramolecular Hydrogen Bonding on the Intensity and Frequency of OH Stretching Band in Alicyclic Substances. *Spectrosc. Lett.* **1976**, *9*, 821–832.

(27) Takasuka, M.; Saito, T.; Yamakawa, M. FTIR Spectral Study of Double Cyclic Intermolecular Hydrogen Bonding in Glutaric Acids. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1513–1516.

(28) Takasuka, M.; Ezumi, K.; Yamakawa, M. FTIR Spectral Study of Hydrogen Bonding in ω-Alkanedicarboxylic Acids in Dilute CCl_4 Solution. *J. Chem. Soc., Perkin Trans. 2* **1992**, 29–33.

(29) Ohtani, M.; Narisada, M. Synthesis and in Vitro Activity of Stereoisomers of a Novel Thromboxane Receptor Antagonist, (±)-(5Z)-7-[3-*endo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic Acid. *J. Med. Chem.* **1990**, *33*, 1027–1031.

(30) (a) Dallinga, G.; Toneman, L. H. Electron Diffraction by Gases: The Molecular Structure of Bicyclo[3.1.1]heptane. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 185–192. (b) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. Critical Evaluation of Molecular Mechanics. *J. Am. Chem. Soc.* **1973**, *95*, 8005–8025. (c) It was presumed that the ρ value of pinane-TXA$_2$ (PTA$_2$)[53] with a 6,6-dimethylbicyclo-[3.1.1]heptane ring is lower than that of U-46619, because the stability of the conformer of the diequatorial type in PTA$_2$ decreases due to the steric interaction between the *endo*-6-methyl group and the hydrogen atom at the carbon atom attached to the ω-side chain. This ρ value is estimated to be 66% at 2.2305×10^{-5} M in CCl_4 solution. This result suggests that PTA$_2$ contains two conformers of the diequatorial and the diaxial types. PTA$_2$ (TXA$_2$ receptor antagonist)[53] was obtained commercially from Cayman Chemical Co.

(31) Cimino, G.; Spinella, A.; Sodano, G. Naturally Occurring Prostaglandin-1,15-lactones. *Tetrahedron Lett.* **1989**, *30*, 3589–3592.

(32) In spite of the fact that 1 and 1′ have the 11- and 15-hydroxyl groups, the intensities of the ν_{OH} bands at 3624 and 3606 cm^{-1} for these hydroxyl groups are similar to those at 3623 cm^{-1} (ϵ = 42) and 3602 cm^{-1} (ϵ = 48) of **2** (N = 82%) which has only the 11-hydroxyl group. The total A values of these ν_{OH} bands observed for 1, 1′, and **2** are 26.4, 28.3, and 24.8×10^{-8} cm^2 s^{-1} molecule^{-1}, respectively. The value of 1 and 1′ is slightly larger than that of **2**. If the 15-hydroxyl group of 1 and 1′ did not form the intramolecular hydrogen bonds as in (A), its free ν_{OH} band would appear at ca. 3619 cm^{-1} because the ν_{OH} bands of 1-octen-3-ol are observed at 3619 cm^{-1} (ϵ = 71) and 3601 cm^{-1} (ϵ = 7), which are assigned to the free ν_{OH} and intramolecular OH···π hydrogen-bonded ν_{OH} bands, respectively. These results indicate that the free ν_{OH} band of the 15-hydroxyl group in 1 and 1′ almost disappeared. Accordingly, the ν_{OH} bands at ca. 3624 and 3606 cm^{-1} are assigned to the free 11-hydroxyl group and the 11-hydroxyl group intramolecularly hydrogen-bonded to the π-electrons on the 9-carbonyl group, respectively.[26b,c] However, the latter band is not discussed because the bonding is very weak, although its intensity is comparable to that of the former band.

(33) Because the intensities of the cyclic intramolecular hydrogen-bonded ν_{OH} bands as in (A) are very small,[20] their bands cannot be obtained unequivocally when the ρ value is small.

(34) For compounds **3** with the 9- and 15-hydroxyl groups and **4** with the 9-hydroxyl group, an almost symmetrical ν_{OH} band was observed at 3627 cm^{-1} in the region of more than 3600 cm^{-1}, indicative of the free ν_{OH} band for the 9-hydroxy group. This suggests that the free ν_{OH} band for the 15-hydroxyl group[32] in **3** almost disappeared. The intensity (ϵ = ca. 61) of the free ν_{OH} band at 3627 cm^{-1} in 4 was smaller than that (ϵ = ca. 103) of **3**.

(35) Compound **5** gives two free ν_{OH} bands at 3625 and 3611 cm^{-1}. The former and latter bands were assigned to the 9- and 15-hydroxyl groups, respectively, because the former corresponded to a symmetrical free ν_{OH} band at 3626 cm^{-1} for the 9-hydroxyl group in **6**. The ϵ value of 100% free ν_{OH} band of **6** was estimated to be 97 from the N value. The ϵ values of the free ν_{OH} bands for the 9-hydroxyl group in **5** and **6** were 85 and 61, respectively. These findings indicate that the intensities of these bands decreased. For **5**, the ρ values were estimated to be 13 and 46% from the ϵ values of the free ν_{OH} band for the 9-hydroxyl group and the free $\nu_{C=O}$ band for the carbomethoxy group, respectively. This indicates that the 15-hydroxyl group of (46–13)% in **5** is intramolecularly hydrogen-bonded to the carbomethoxy group, and the intensity of its free ν_{OH} band decreases.

(36) Dolton, F.; McDougall, J. I.; Meakins, G. D. Hydroxy-steroids. Part II. The Conformations and Infrared Spectra of Steroid 3,5-Diols and Related Compounds. *J. Chem. Soc.* **1963**, 4068–4075.

(37) The bands at 3559 cm^{-1} in **7** and at 3540 cm^{-1} in **8** are assigned to the 9-hydroxyl group hydrogen-bonded to the 11-hydroxyl group and/or to the 11-hydroxyl group hydrogen-bonded to the 9-hydroxyl group because these bands correspond to the hydrogen-bonded ν_{OH} band at 3544 cm^{-1} in *cis*-cyclopentane-1,3-diol [Kuhn, L. P. *J. Am. Chem. Soc.* **1952**, *74*, 2492].

(38) When an oxygen atom of the hydroxyl group is intramolecularly hydrogen-bonded by other hydroxyl group, the frequency and intensity of its free ν_{OH} band vary.

(39) The intensity (ϵ = ca. 99) of the free ν_{OH} band in **7** is larger than that (ϵ = ca. 45) in **8** because **7** does not form an appreciable amount of the cyclic intramolecular hydrogen bond (A) between the 9-hydroxyl and carboxyl groups and/or 11-hydroxyl and carboxyl groups. The intensity (ϵ = 56) of the free ν_{OH} band at 3615 cm^{-1} in **9** is smaller than the former intensity because the intramolecular hydrogen bond (C) in **9** is formed between these hydroxyl and carbomethoxy groups.

(40) Since the intramolecular hydrogen-bonded ν_{OH} band formed between the hydroxyl groups in **9** is overlapped by that formed between the hydroxyl and carbomethoxy groups, the intensity (ϵ = 70) of its band at 3547 cm^{-1} is larger than that (ϵ = 47) at 3540 cm^{-1} in **8**.

(41) In spite of the fact that **10** has two hydroxyl groups, its compound gave an almost symmetrical free ν_{OH} band at 3615 cm^{-1} (ϵ = 47), indicative of the decrease of the free ν_{OH} bands.

(42) Suga, H.; Hamanaka, N.; Kondo, K.; Miyake, H.; Ohuchida, S.; Arai, Y.; Kawasaki, A. ONO-3708: An Effective Thromboxane A$_2$ Antagonist Possessing 3-Acylaminopinane Skeleton. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1987**, *17*, 799–802.

(43) (a) Ohuchida, S.; Hamanaka, N.; Hayashi, M. A Convenient Route to (+)-(9,11)-Epithia-(11,12)-methano-thromboxane A$_2$ from Prostaglandin E$_2$ Methyl Ester. *Tetrahedron Lett.* **1981**, *22*, 5301–5302. (b) Katsura, M.; Miyamoto, T.; Hamanaka, N.; Kondo, K.; Terada, T.; Ohgaki, Y.; Kawasaki, A.; Tsuboshima, M. In Vitro and In Vivo Effects of New Powerful Thromboxane Antagonists (3-Alkylamino Pinane Derivatives). *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1983**, *11*, 351–357.

(44) Toda, N.; Nakajima, M.; Okamura, T.; Miyazaki, M. Interactions of Thromboxane A$_2$ Analogs and Prostaglandins in Isolated Dog Arteries. *J. Cardiovasc. Pharmacol.* **1986**, *8*, 818–825.

(45) Toda, N. Different Responsiveness of a Variety of Isolated Dog Arteries to Prostaglandin D$_2$. *Prostaglandins* **1982**, *23*, 99–112.

(46) Narumiya, S.; Okuma, M.; Ushikubi, F. Binding of a Radioiodinated 13-Azapinane Thromboxane Antagonist to Platelete: Correlation with Antiaggregatory Activity in Different Species. *Br. J. Pharmacol.* **1986**, *88*, 323–331.

(47) Siegl, A. M.; Smith, J. B.; Silver, M. J.; Nicolaou, K. C.; Ahern, D. Selective Binding Site for [^{3}H]Prostacyclin on Platelets. *J. Clin. Invest.* **1979**, *63*, 215–220.

(48) Miller, O. V.; Gorman, R. R. Evidence for Distinct Prostaglandin I$_2$ and D$_2$ Receptor in Human Platelets. *J. Pharmacol. Exp. Ther.* **1979**, *210*, 134–140.

(49) (a) Hanasaki, K.; Kishi, M.; Arita, H. Phorbol Ester-induced Expression of the Common, Low-affinity Binding Site for Primary Prostanoids in Vascular Smooth Muscle Cells. *J. Biol. Chem.* **1990**, *265*, 4871–4875. (b) Powell, W. S.; Hammarström, S.; Samuelsson, B.; Miller, W. L.; Sun, F. F.; Fried, J.; Lin, C. H.; Jarabak, J. Interactions between Prostaglandin Analogues and a Receptor in Bovine Corpora Lutea. *Eur. J. Biochem.* **1975**, *59*, 271–276.

(50) Bundy, G. L.; Kimball, F. A.; Robert, A.; Aiken, J. W.; Maxey, K. M.; Sebek, O. K.; Nelson, N. A.; Sih, J. C.; Miller, W. L.; Hsi, R. S. P. Synthesis and Biological Activity of 9-Deoxo-9-Methylene and Related Prostaglandins. *Adv. Prostaglandin Thromboxane Res.* **1980**, *6*, 355–363.

(51) The intensities of the free ν_{OH} band for the 15-hydroxyl group[32] and for the carboxyl group at 3530 cm^{-1} (ϵ = 23) greatly decreased. The 11-hydroxyl group gives two ν_{OH} bands, with peaks at 3625 and 3605 cm^{-1} which are similar to those of **2**.[32]

(52) This value is in close accord with the ρ value of 1, suggesting that the intramolecular hydrogen bond is scarcely formed between the 9-carbonyl and carboxyl groups as mentioned in 1.

(53) Nicolaou, K. C.; Magolda, R. L.; Smith, J. B.; Aharony, D.; Smith, E. F.; Lefer, A. M. Synthesis and Biological Properties of Pinane-thromboxane-A$_2$, a Selective Inhibitor of Coronary Artery Constriction, Platelet Aggregation, and Thromboxane Formation. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2566–2570.