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APPLICATION OF PHYSICAL METHODS TO SOME STRUCTURAL AND STEREOCHEMICAL PROBLEMS IN THE PROSTAGLANDIN FIELD

PIERRE CRABBÉ*
Joint Contribution from the Research Laboratories, Syntex, S.A. and the Facultad de Quimica, Universidad Nacional Autonoma de Mexico, Mexico

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Abstract—The combination of various physical methods allows to solve structural and stereochemical features associated with a number of novel prostaglandins. These examples illustrate the usefulness of physical techniques in solving problems related to modified prostaglandins obtained either by total synthesis or by reactions performed on the natural PGA_2 molecule.

Résumé—Les méthodes physiques permettent d'établir sans ambiguïté la structure et la configuration de quelques nouvelles prostaglandines, préparées soit par synthèse totale, soit à partir de la PGA_2, isolée des coraux de la famille *Plexaura homomalla.* En particulier, on montre que l'application de réactif de déplacement chimique en résonance magnétique nucléaire, ainsi que les méthodes chirales permettent de résoudre aisément un certain nombre de problèmes stéréochimiques liés à de telles molécules.

The prostaglandins form a class of natural substances which are remarkable by their ubiquity in mammals, as well as by their broad spectrum of biological activities.[1] Although some properties have been recognized more than thirty years ago, the structure elucidation of prostaglandins and hence their chemistry are fairly recent. This is due mainly to technical difficulties encountered in their isolation and to the dramatic development of antibiotics and hormone therapy during that period.[2-9]

So far, prostaglandins (PG) have been found in low concentrations in numerous tissues, organs and fluids of mammals.[2-9] One has also isolated PG from the soft coral *Plexaura homomalla* (Esper)[10] found in the Caribbean. Finally, a recent report mentions a possible source of PGA_1 from plant origin, *i.e.* yellow onion source.[11]

Natural PG have a 5-membered ring bearing alkyl chains at positions 8 and 12. Their structural differences are due to the nature of the oxygen function at C-9 and to varying degrees of bond unsaturation. Reports of extensive studies relating structural changes with dramatic biological variations appear with increasing frequency. Hence, the relevance of PG configuration and conformation to biological activity has become widely recognized. Chain–chain interactions, the nature of the functional groups and the configuration of substituents on the pentane ring are the major intramolecular factors governing the overall conformation of the PG and controlling the relative positions of possible functional sites.

The prostaglandin field has been shown to be fruitful in development of useful isolation techniques, in adequate utilization of physical methods for structural and stereochemical purposes, in clever application of known synthetic methods, as well as imagination and development of novel chemical reactions. In particular, the determination of structure of the primary PG was achieved in a relatively short time, by ingenious and careful work involving degradations and appropriate use of physical methods.[1,12] In this respect, the brillant work of the Swedish School emphasizes the usefulness of combination between gas chromatography and mass spectrometry.[1,12,13] For some of the natural PG there exists a method requiring combined vapor phase chromatography and mass spectrometry, with the use of deuterated PG as internal standards and multiple-scanning techniques coupled with on-line computer control.[13] The precise conformation of different PG has been examined by X-ray crystallography.[14] Radioimmunoassays are also frequently used.[15] Moreover, various chromatography techniques[16] are widely utilized, as well as mass spectrometry[13,17] and NMR spectroscopy.[18]

Although various review articles have covered the chemistry of PG and approaches to their total synthesis,[4-8,19-25] it should be emphasized that the elaboration of the PG molecule with the correct

*Present address: C.E.R.M.O., Université Scientifique et Médicale, Boîte Postale 53, Grenoble 38041, France.

structural and stereochemical features constitute a formidable task, so far accomplished by many laboratories.

One of the elegant syntheses by Corey *et al.* is of particular interest,[26] because the F_α, E, A, C and B prostaglandins of the first, second and third series can be prepared stereoselectively from appropriate intermediates.[27] In addition, the flexibility of this synthetic scheme[26,27] also allows to prepare a number of modified prostaglandins[28,29] Indeed, various laboratories are actively engaged in research programmes having as their main objective the chemical synthesis of modified PG, since it is anticipated that some new entities will exhibit higher and/or more selective biological activity than their naturally occurring counterparts.[28-30]

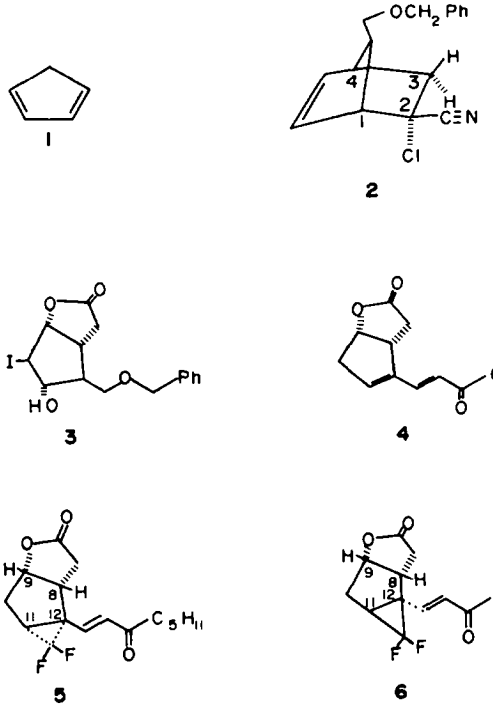
Two routes are commonly used to prepare modified PG. The first one utilizes a total synthetic scheme, often involving novel chemistry, and introduces variations in order to obtain analogues. The second approach uses the naturally occurring PG from the gorgonian of marine coral,[10] as starting material.

During the total synthetic scheme, leading from cyclopentadiene (**1**) to the iodolactone intermediate (**3**),[26] the chloronitrile (**2**) was isolated, and its stereochemistry established. The *exo*-configuration of the nitrile group could be securely assigned by NMR spectroscopy.[31] The NMR spectrum of **2** shows a doublet of doublets (d, $J_1 = 4$ Hz, $J_2 = 14$ Hz) centred at 2·72 ppm and a doublet ($J = 14$ Hz) at 1·7 ppm. The 2·72 ppm signal corresponds to the 3-*endo*-H, which interacts with the 3-*exo*-H and the allylic proton at C-4. The doublet centered at 1·7 ppm corresponds to the 3-*exo*-H which interacts only with the 3-*endo*-H, but not with the allylic proton, since the diedral angle between them is 90°. Moreover, the 3-*exo*-H appears at higher field, because it is located in the shielding cone of the nitrile group.

NMR spectroscopy proved also very useful for the assignment of configuration to the difluoromethylene bridge in the isomeric tricyclic compounds (**5** and **6**), the key intermediates in the synthesis of novel difluoromethylene PG.[32]

The dienone (**4**), typified by its characteristic UV absorption at λ_{max} 274 nm (log ϵ 4·25), is readily prepared[32] from a known compound.[26] Addition of difluorocarbene to this dienone (**4**), which incidentally is also an intermediate for the synthesis of PG belonging to the C-series,[33] affords a mixture of isomers (**5** and **6**).

Both isomers exhibit identical UV [λ_{max} 238 nm (log ϵ 4·17)] and very similar IR spectra. The β-configuration of the difluoromethylene bridge in the intermediate (**6**) is supported by the NMR of the 8β proton which appears as a doublet ($J = 8$ Hz) at 3·33 ppm, attributed to long range coupling with a fluorine of the difluorocyclopropyl grouping. This coupling is absent in the α-difluorocyclopropyl isomer (**5**).[32] Thus, although regiospecific, the difluorocarbene addition to compound (**4**) is not stereoselective.



1 2 3 4 5 6

During work on the synthesis of modified PG by photochemical addition reactions to PGA_2 (**7a**),[34] one faced the problem of assigning the correct configuration of the C-5 as well as the C-13 double bonds after irradiation, for it is known that photochemical processes can induce isomerization of olefins.[35] One of the safest ways to ascertain the geometry of a double bond is to determine the coupling constant of the olefinic protons. However, since the chemical shifts observed under usual conditions are very similar in the PG series, it is sometimes hazardous to draw conclusions from these NMR spectra. In order to circumvent this problem, the geometry of the double bonds of various PG before and after irradiation was investigated with the complex with tris (dipivalomethanato) europium (III)[36] (see below).

The NMR spectrum of PGA_2 methyl ester (**7b**) is first obtained under usual conditions and the chemical shifts of most protons of the molecule are identified.[36] A precise amount of $Eu(DPM)_3$ is then added to the solution and the NMR spectrum is redetermined. First, this allows to get a much better resolution of most chemical shifts. Second, the separation of the signals now permits to establish the precise coupling constants, further confirmed by double and triple resonance experiments, using two audio-oscillators.[36]

Surprisingly, little has been published on the chiroptical properties of PG and their synthetic intermediates.[37] One reason for this lack of information may be that most PG studied so far are obtained by total synthetic schemes in which the resolution step occurs late in the sequence.

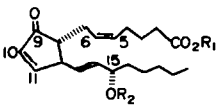
Photochemical cycloaddition in methylene chloride solution at low temperature, of ethylene to the PGA_2 derivative (**7b**), from the marine corals,[10] affords a mixture of photoadducts, separated by preparative TLC.[34] The UV, IR and NMR properties of the 10β, 11β-cyclo-adduct (**8b**) are reminiscent of these of its α-cyclobutyl isomer (**8a**). However, the β-adduct (**8b**) exhibits an intense negative Cotton effect in the 300 nm region ($[\theta]_{304}$ − 10,800) (MeOH), since the cyclobutane falls into a negative octant.[38] In contrast, the α-adduct (**8a**) shows a much weaker negative Cotton effect ($[\theta]_{302}$ − 2,050) (MeOH).

Thus, the chiroptical properties confirm that during the irradiation reaction, neither did isomerization of the C-5 or C-13 double bond occur, nor did epimerization take place at position 8, since 8-*iso*-PGE derivatives are known to display an intense positive Cotton effect in the 300 nm region.[39]

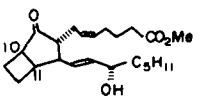
Similarly, light induced cycloaddition of PGA_2 methyl ester (**7b**) to allene yields a mixture of isomeric (methylene) 10,11-ethylene-11-desoxy-PGE_2 methyl esters (**9** and **10**). In addition to the cyclopentanone like carbonyl absorption (ν_{max} 1745 cm^{-1}) in the IR spectrum of these isomers, their NMR spectra confirm the structures. The NMR signals of *exo*-methylene protons in compound (**9**) appear at 4·90 and 5·02 ppm and thus are similar to these of (3′-methylene) 2,3-ethylenecyclopentanone (**11**).[40] Moreover, the configuration of the methylene cyclobutane bridge appears to be α in the new PG (**9**), because its negative Cotton effect {$[\theta]_{302}$ − 5,570) (MeOH); a − 64 (dioxan)} is reminiscent of that exhibited by the cyclobutylderivative (**8a**) (see above).

As in the case of (2′-methylene) 2,3-ethylenecyclopentanone,[40] the structure of the photoadduct (**10**) is based on the appearance of *exo*-methylenic protons at 4·79 and 4·95 ppm in the NMR spectrum, and its UV maximum at λ_{max} 302 nm (log ϵ 2·39), typical of a β,γ-unsaturated keto-system. Additionally, the β-configuration of the newly introduced cyclobutane unit in the prostanoic ester (**10**) is supported by the intense negative chiroptical properties associated with the homo-conjugated chromophore {$[\theta]_{304}$ − 14,850) (MeOH), *a* − 142 (dioxan)}. This is in agreement with the extension of the octant rule for β,γ-unsaturated ketones,[41] as the methylenecyclobutane moiety lies in the upper-right negative octant.

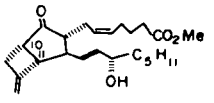
The NMR shift reagent was also used with the photoadducts (**8a**, **8b**, **9** and **10**).[36] The coupling constants of the vinylic protons at C-5 and C-6 are the same in compound (**7b**) as in the cyclo-adducts (**8** to **10**), ($J_{5,6}$ = 11 Hz), thus confirming that no isomerization of the *cis*-double bond has occurred during the photochemical processes. Since the coupling constant of the vinylic protons at C-13 and C-14 is the same ($J_{13,14}$ = 15 Hz) in compounds (**7b** to **10**), by similar reasoning, one can deduce that the *trans*-geometry of this double bond is also preserved during the photocondensation reactions.



7 a: $R_1 = R_2 = H$
b: R_1 = Me ; R_2 = H
c: R_1 = Me ; R_2 = Ac



8 a: 10βH, 11βH
b: 10αH, 11αH



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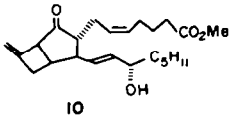

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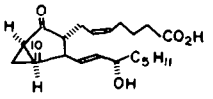

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These observations emphasize the usefulness of the shift reagent for stereochemical assignments around a double bond. Furthermore, the NMR spectra obtained with this shift reagent complex allow to identify most protons of the PG molecule. This is useful for the resolution of the challenging structural and stereochemical problems encountered during the total or partial synthesis of novel entities belonging to this class of natural products.

Besides the photochemical addition of two- or three-carbon units to positions 10 and 11 of the PG molecule, a methylene group is also introduced, thus yielding a 10,11-cyclopropyl-PG.[42] Reaction of PGA_2 1-methyl ester 15-acetate (**7c**) with diazomethane in ether furnishes a pyrazoline derivative, which by irradiation followed by hydrolysis provides the cyclopropyl-PG (**12**). The β-configuration of the 10,11-methylene group in the bicyclic PG (**12**) is deduced from its mode of formation,[42] as well as its chiroptical properties. Compound **12** presents a weakly positive CD curve ($[\theta]_{300}$ + 500) reminiscent of that shown by the 10β,11β-epoxide (**13b**). Contrastingly, the isomeric α-epoxide (**13a**) displays a negative Cotton effect in the same spectral region.[43]

In addition, the positive molecular ellipticity exhibited by the modified PG (**12**) supports the

β-configuration assigned to the cyclopropyl group. The 10,11-methylene being located in the upper-right octant, gives rise to a positive Cotton effect, in agreement with the reverse octant rule for α-cyclopropyl and α-epoxy-ketones.[44]

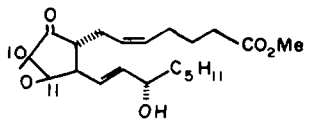
As indicated earlier, PGA_2 methyl ester (**7b**) from the marine coral provides an unusual opportunity for 1,4-addition reactions.[45] Conjugate addition of lithium dimethyl copper[46] to the ester (**7b**) affords the 11α-methyl 11-deoxy PGE_2 methyl ester (**14a**). The configuration of the newly introduced methyl group is α, since the alkyl PG (**14a**) exhibits a negative Cotton effect ($[\theta]_{299} - 10{,}100$), reminiscent of that shown by PGE_2,[37] as well as by other 11α-substituted PGE_2 analogues. Indeed, various 11α-substituted PGE_2 derivatives, also obtained by Michael-type addition reactions,[47] such as the 11α-nitrile (**14b**; $[\theta]_{298} - 9{,}990$) and the 11α-thio-ether (**14c**; $[\theta]_{298} - 8{,}980$), display a more intense negative Cotton effect than their 11β-counterparts, like the 11β-cyano derivative (**15a**; $[\theta]_{296} - 6{,}300$) (all CD curves in MeOH solution).

The 11-nitromethyl-PG (**14d** and **15b**)[47] constitute a special case, as besides the 9-keto chromophore, they possess the nitro-group which is optically active in a dissymmetric surrounding.[48] Additionally, the ketone and the nitro-chromophores, situated close to each other, probably interact in compounds (**14d**) and (**15b**).[48,49] As a result, whereas the 11α-isomer (**14d**) exhibits positive chiroptical properties ($[\alpha]_D + 12°$; $[\theta]_{294} + 2{,}770$), a negative Cotton effect ($[\alpha]_D - 95°$; $[\theta]_{296} - 10{,}070$) is associated with the 11β-isomer (**15b**).

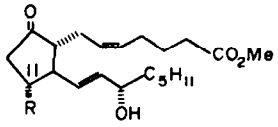
A careful examination of the data of natural PG reported in the literature indicate that sometimes substantial discrepancies appear in their specific rotation values. These discrepancies induced us to examine the CD curves of some modified PG at various temperatures, and in solvents of different polarity. As could be expected from the structural features of the PG molecule, sizeable variations have been noted.*

For example, the molecular ellipticity of the CD curve of the 11α-methyl analogue (**14a**) varies from $[\theta]_{299} - 10{,}100$ at room temperature to $-10{,}500$ at $-40°$, $-11{,}000$ at $-80°$, $-11{,}250$ at $-120°$, $-11{,}600$ at $-160°$ and $[\theta]_{307} - 12{,}600$ at $-180°$, *in extenso* the intensity of the negative Cotton effect increases with a decrease of the temperature. Additionally, one observes definite changes in the fine structure associated with the carbonyl chromophore in these CD curves.* Similarly, changes in the nature of the solvent can induce substantial modifications in the intensity of the experimental Cotton effects, *e.g.* the molecular ellipticity of the methylated PG (**14a**) varies from $[\theta]_{299} - 10{,}100$ in MeOH to $[\theta]_{306} - 12{,}880$ in chloroform solution.* This is attributable to variations in the conformation of the cyclopentanone unit and/or to changes in the population of side chain conformers (and rotamers), as well as to other factors such as inter- and intramolecular interactions (*e.g.* hydrogen bonding, etc).*

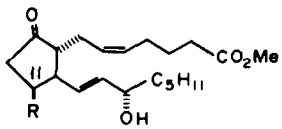
*Full details on the CD results obtained with natural and modified PG will be published at a later date.



13 a: 10βH,11βH
b: 10αH,11αH



14 a: R = Me
b: R = CN
c: R = S-C_2H_5
d: R = CH_2NO_2



15 a: R = CN
b: R = CH_2NO_2

The combination of different physical methods, in particular NMR, CD and mass spectrometry (MS) has allowed to establish both the structure and stereochemistry of substituted tricyclic substances obtained by intramolecular enone-ene photocyclization reactions with PGA_2 methyl ester (**7b**).[50] Irradiation of the enone (**7b**) with a Hanau Q-18 high pressure UV lamp, at $-70°$ for 90 min in tetrahydrofuran solution, affords a mixture of three isomeric photoadducts in *ca* 48% yield, besides 20% of recovered starting material.[51]

Preparative TLC allows to separate the saturated ketone (**18**) as the major component. Its structure is supported by the presence of an IR band at 1755 cm^{-1}, typical of similar cyclopentanones,[52] the absence of intense UV absorption above 220 nm and the NMR which shows only two olefinic protons at *ca* 5·48 ppm, compared to six in its precursor (**7b**). Also in agreement with the tricyclo[3, 1, 1, 1] octanone structure (**18**), is the CD curve which presents a weakly negative Cotton effect ($[\theta]_{306} - 460$), because the molecule is almost symmetrical, but for the chain, *i.e.* the chain at C-12

falls essentially in a symmetry plane of the carbonyl, whereas the four carbon chain at C-5 seems to be located, at least partly in a front octant.

The second substance is the tricyclic derivative (**21**). In this compound the saturated carbonyl is located in a 6-membered ring, so that the ketone and the methyl ester IR absorption bands appear in the same region (ν_{max} 1730 cm^{-1}). Moreover, ketone (**21**) shows only two olefinic protons in the NMR spectrum and displays a positive CD curve ($[\theta]_{295}$ + 5,640), since the C-12 carbon atom is twisted in a positive octant.

The third and minor component of this reaction is a stereoisomer of the tricyclic substance (**21**). Structure **22** is assigned to it. Its physical properties are reminiscent of these of its configurational isomer (**21**), so that compound **22** also exhibits a positive Cotton effect ($[\theta]_{295}$ + 5,150).

These three photoadducts present the molecular ion peak at *m/e* 348 (M^+) under electron impact. They also show the same fragment at *m/e* 234 corresponding to the loss of carbon C-5 with its chain (114 mass units). Conversely, the isomeric compounds (**21** and **22**) give a peak *m/e* 193, corresponding to M^+-155 in which 155 is the loss of C-1 to C-9. This cannot and does not occur in the fragmentation pattern of compound **18**.

The formation of the major compound (**18**) can be rationalized as resulting from an intramolecular photochemical addition process, due to the stereoproximity of the *cis*-double bond at C-5 and C-6 which adds to positions C-11 and C-10, respectively, from the α-side of PGA_2 methyl ester in conformation (**16**), through the stable biradical (**17**).[53]

The isomers (**21** and **22**) result from a regioselective internal photoinduced α-addition of the *cis*-double bond located at positions 5 and 6 of conformation (**19**), to C-10 and C-11, respectively. The initial bond is formed between C-6 and C-11, and the diradical intermediate (**20**) is rotationally equilibrated before ring closure.[54]

During the above mentioned photochemical addition reactions of ethylene and allene to compound **7b** in methylene chloride solution,[34] no internal cycloaddition was detected. This may be attributed to the nature of the solvent,[53] the absence of external substrate with which to react and/or to the fact that while the previously mentioned cycloadditions were very fast processes, these intramolecular photochemical additions are slower reactions, thus allowing the formation of the requisite biradicals (**17** and **20**).

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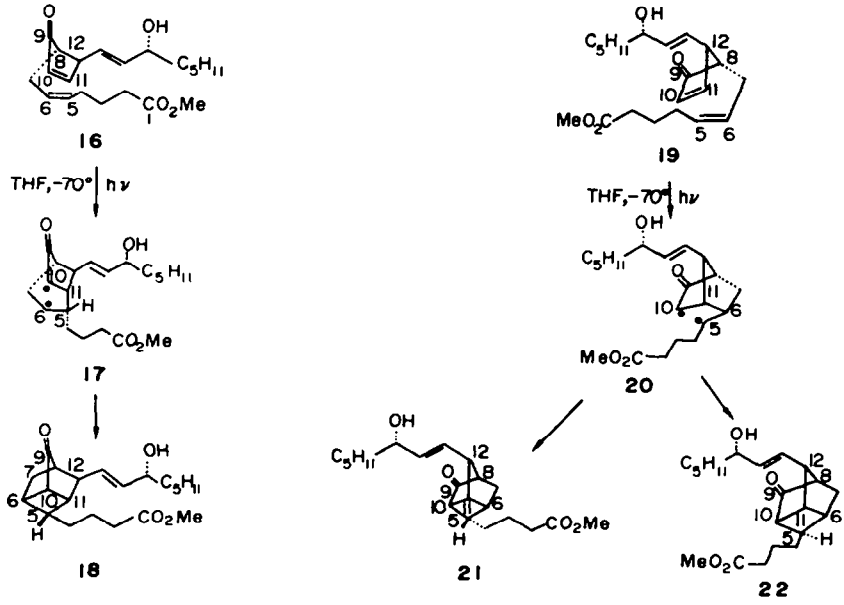

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