et al., on a related system.[3a] The [1,5] hydrogen transfer reaction **3** → **8** should proceed most easily suprafacially,[14] *i.e.*, a thermal process if concerted, but is observed to be unquenched by cooling.

All of the observed hydrogen transfer reactions are reasonable pathways by which the benzohexatrienes may recover aromaticity, as are the observed photochemical Diels–Alder reactions. In contrast, the cis–trans isomerization reactions **1** ⇄ **2**, **3**, which do not have the thermodynamic incentive of recovery of aromaticity, are not observed at low temperature, as shown by the nearly mutually exclusive product mixtures in the low-temperature experiments. The thermal analog, which apparently does not occur either, is unreasonable and unprecedented.

In this example, the photochemical Diels–Alder reaction has been given a fair chance to demonstrate concertedness, which it failed to do. In light of this result and the very different photochemical Diels–Alder reaction of Padwa and Clough,[1] in which at least partial electronic control was demonstrated, it is clear that one must not depend on orbital symmetry control of stereoselectivity in exploiting this reaction.

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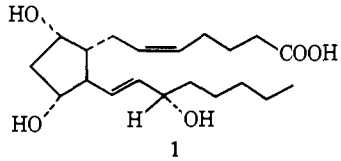
Structure of a Deoxyprostaglandin in Man

Sir:

Prostaglandin $F_{2\alpha}$($PGF_{2\alpha}$) (**1**) has been shown to have



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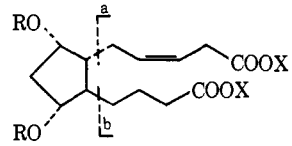


2, X = H; R = H
3, X = CH_3; R = H
4, X = CH_2CH_3; R = H
5, X = CH_3; R = $(CH_3)_3Si$
6, X = CH_3; R = CH_3CO
7, X = CH_2CH_3; R = $(CH_3)_3Si$
8, X = CH_2CH_3; R = CH_3CO
9, X = CH_3; R = $(C^2H_3)_3Si$

many biological effects of which the actions on the uterus and corpus luteum have been studied extensively.[1] The structures of several metabolites of $PGF_{2\alpha}$ in humans and experimental animals were recently determined.[2a,b] The metabolites consisted of C_{18}, C_{16}, and C_{14} derivatives formed by the action of 15-hydroxyprostanoate dehydrogenase, Δ^{13}-reductase, and β and ω oxidation systems. We now wish to report the isolation and structure of metabolite **2** formed by the reactions mentioned above and, in addition, elimination of the oxygen function originally at C-15.

[9β-^{3}H]$PGF_{2\alpha}$ (35 μg, specific activity 0.6 μCi/μg) was administered intravenously to female subjects. The radioactive urine was added to urine containing unlabeled metabolites from administration of 20 mg of $PGF_{2\alpha}$ and the metabolites were isolated and separated as described in detail recently.[2a] Material in peak II (compound II) (see ref 2a) containing about 20% of administered radioactivity was treated with diazomethane and chromatographed with solvent system F-50, where 90% of the applied radioactivity appeared with 250–330 ml of effluent (18-g column). This material was further purified by thin-layer chromatography and silicic acid chromatography. Material in peak II was also treated with diazoethane to give the ethyl ester.[3]

The methyl (**3**) and ethyl (**4**) esters were converted into trimethylsilyl ether derivatives and acetates and analyzed by radio glc. The difference in retention time (1.2 C) between **5** and **7** and between **6** and **8** indicated that compound II was a dicarboxylic acid and the difference (1.1 C) between **5** and **6** and between **7** and **8** indicated the presence of two hydroxyl groups.[3]

In the mass spectrum of **5** (Figure 1) the ion with the highest *m/e* value appeared at *m/e* 458. The presence of two hydroxyl groups in compound II was supported by prominent ions at *m/e* 368 (M − 90) and 278 (M − (2 × 90)). Ions at *m/e* 267 and 255 were interpreted to be formed by loss of trimethylsilanol and the side chains attached to C-6 (a) and C-10 (b), respectively. An ion at *m/e* 217, [TMSiO=CHCH=CHOTMSi]$^+$, indicated that the cyclopentanediol part of the molecule was retained. An ion (*m/e* 227) with important structural implications was interpreted to be due to [TMSiO=CHCH=CHCH=$CHCH_2COOCH_3$]$^+$ and to be formed by cleavages between C-7 and C-8 and between C-6 and C-10. The mass spectrometric interpretations were supported by high-resolution mass spectrometry,[4] deuterium labeling of the trimethylsilyl groups (**9**), and the use of [3,4,6,9,10,12-D_6] compound II obtained by administering [5,6,11,12,14,15-D_7]$PGF_{2\alpha}$.[5] Additional support for the proposed structure and for the interpretations described above was obtained by mass spectrometric analysis of **6**, **7**, and **8**.

Compound II did not react either with borohydride or with methoxyamine which indicated the absence of a keto group. The presence of a double bond was established by catalytic hydrogenation of **6** and mass

(1) For references see "Prostaglandins," *Ann. N.Y. Acad. Sci.*, 180 (1971).
(2) (a) E. Granström and B. Samuelsson, *J. Biol. Chem.*, 246, 5254 (1971); *ibid.*, 246, 7470 (1971); E. Granström, *Eur. J. Biochem.*, 25, 581 (1972); (b) E. Granström and B. Samuelsson, *ibid.*, 10, 411 (1969); K. Gréen, *Biochim. Biophys. Acta*, 231, 419 (1971).
(3) Methods for chromatographic separations and characterization of functional groups by glc are described in detail in ref 2a.
(4) The following ions were analyzed: *m/e* 368 (calcd for $C_{19}H_{32}SiO_5$, 368.2018; found, 368.2004 (−3.8 ppm)), 278 (calcd for $C_{16}H_{22}O_4$, 278.1518; found, 278.1518 (±0 ppm)), 267 (calcd for $C_{14}H_{23}SiO_3$, 267.1416; found, 267.1425 (+3.3 ppm)), 225 (calcd for $C_{13}H_{23}SiO_3$, 255.1416; found, 255.1409 (−2.7 ppm)), and 227 (calcd for $C_{11}H_{19}SiO_3$, 227.1102; found, 227.1113 (+4.8 ppm)). The equipment used was an Atlas SM 1 high-resolution mass spectrometer and a Gaertner spectrum plate comparator. We are indebted to Dr. R. Ryhage and Mr. R. Hjälm for the analyses.
(5) In agreement with previous results (M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, 246, 1073 (1971)) the deuterium atom originally at C-15 was lost by oxidation occurring in connection with reduction of the Δ^{13} double bond.

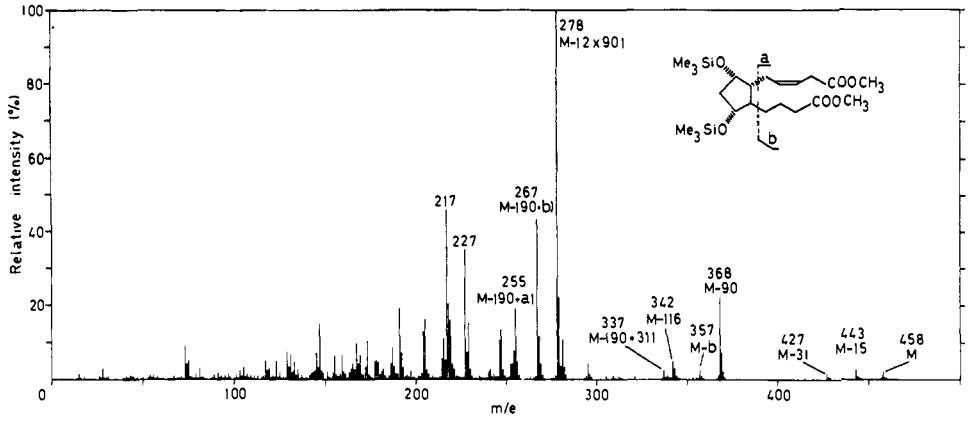
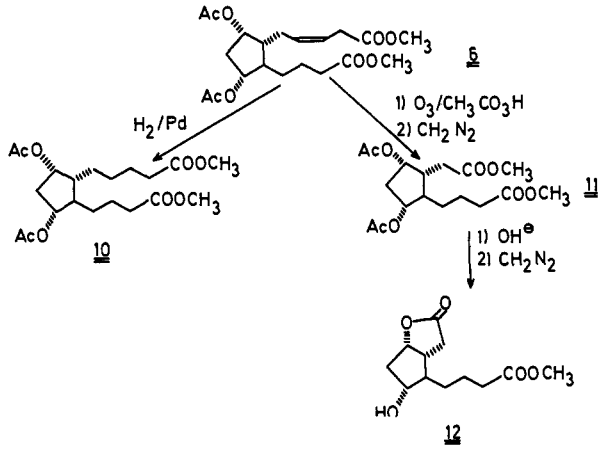


Figure 1. Mass spectrum of **5**.

spectrometric analysis of the product **10**. The position of the double bond was studied by oxidative ozonolysis of **6**. The *C* value (18.7; decrease of 2.8) and the mass spectrum of the esterified product **11** were consistent with a Δ^3 double bond in compound **11**. However, although the mass spectrum of **11** showed ions at *m/e* 183 (M − (60 + 42 + 73)) and 165 (M − (2 × 60 + 73)) indicating the presence of a C_2 side chain (73), the alternative retention of the Δ^{13} double bond of $PGF_{2\alpha}$ would also give ozonolytic elimination of three carbon atoms and a product of very similar structure. This ambiguity was resolved by analysis of the product obtained by subjecting **11** to alkaline hydrolysis, extraction



with Amberlite XAD-2, and esterification. The infrared spectrum, recorded in chloroform (strong absorptions at 5.66 (saturated γ-lactone) and at 5.78 μ (carbonyl of the carbomethoxy group)), of the product **12** and the mass spectrum of its acetate (ions of high intensities at *m/e* 241 (M − 43), 224 (M − 60), 211 (M − (31 + 42)), 192 (M − (60 + 32)) and 183 (M − 101)) established the γ-lactone structure of **12** and thus conclusively demonstrated the position of the double bond.

On the basis of the data presented it is concluded that compound II is 7α,9α-dihydroxy(dinor,ω-tetranor)-prost-3-ene-1,14-dioic acid (**2**).

We have also demonstrated the occurrence of endogenous metabolite **2** in humans. The reactions involved in the formation of **2** are of particular interest and enzymatic work is in progress to study the mechanism of the elimination of the hydroxyl group during transformation of **1** into **2**.[6]

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Lanthanide-Induced Changes in Proton Spin–Spin Coupling Constants[1]

Sir:

Since 1969, when Hinckley[2] first introduced the application of lanthanide shift reagents (LSR) into nmr spectroscopy, over 130 publications have appeared describing uses of these compounds. One very important application afforded by the great spectral simplification provided by these reagents is the measurement of nuclear spin–spin coupling constants difficult, or impossible, to obtain because the relevant resonances are either obscured or the spectrum is too complicated to make the extraction of these parameters practical. Adding a LSR to a solution "spreads out" the spectrum, often into a first-order pattern, and eliminates the above difficulties. It is the purpose of this communication to report that some caution must be exercised in extracting coupling constants *via* lanthanide-induced shifts (LIS).

In this communication, observed effects of LSR's on coupling constants are reported for two substrate molecules and for the two most popular europium shift reagents, europium(III) tris-2,2,7,7-tetramethyl-3,5-heptanedione and europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione (hereafter, Eu(DPM)$_3$ and Eu(FOD)$_3$, respectively). The first substrate studied[3] was 3,5,5-trimethyl-3-(*p*-chlorophenyl)-cyclohexanone (I),[4] chosen since its structure is now

(1) Lanthanide-Induced Shifts in Proton Nuclear Magnetic Resonance Spectra. II. For part I, see B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281 (1971).

(2) C. C. Hinckley, *ibid.*, **91**, 5160 (1969).

(3) Spectra were run on a Varian HA-100 spectrometer (probe temperature 30°) with the coupling constants being measured at a 50-Hz sweep width and a 0.5 Hz/sec sweep rate. Molecular sieve dried CCl_4 was the solvent in all cases.

(4) I was prepared by the cuprous-catalyzed conjugate addition of *p*-chlorophenylmagnesium bromide to isophorone, analogous to several