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
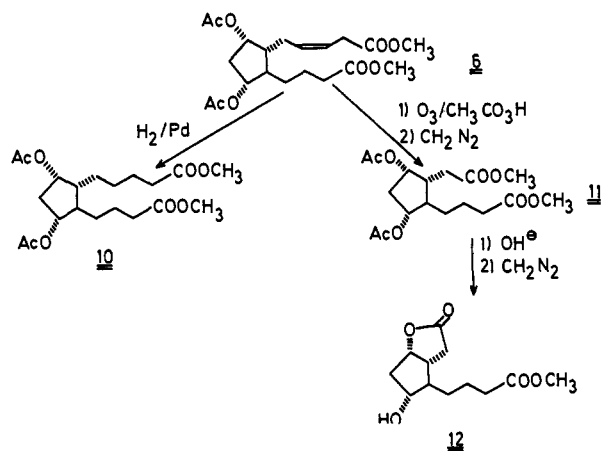
with Amberlite XAD-2, and esterification. The infrared spectrum, recorded in chloroform (strong absorptions at 5.66 (saturated γ-lactone) and at 5.78 μ (carbonyl of the carbomethoxy group)), of the product **12** and the mass spectrum of its acetate (ions of high intensities at m/e 241 (M − 43), 224 (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 $7\alpha,9\alpha$-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 mecha-

nism 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 CCl₄ 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
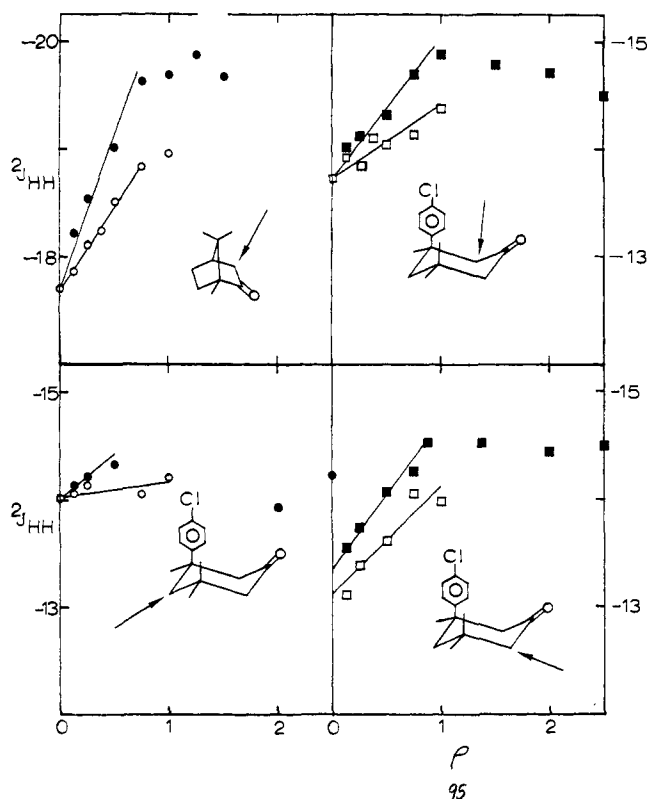
Figure 1. Plots of various geminal methylene H–H coupling constants *vs.* the molar ratio of LSR to substrate, ρ Open circles and squares represent data for Eu(DPM)$_3$; solid black points, data for Eu(FOD)$_3$. The arrow in each structure denotes which protons are plotted.

The four geminal couplings measured in this work all increased in *magnitude* with increasing ρ, or, considering the absolute signs of the constants, became more *negative*. This is quite consistent with effects observed for electron-withdrawing substituents on carbonyl compounds,[6] in this case that role being played by a

Table I. Geminal Methylene H–H Coupling Constants[a] of I and II at Various Molar Equivalents of LSR

ρ^b	I $^2J_{HH}$(C-2)	I $^2J_{HH}$(C-4)	I $^2J_{HH}$(C-6)	II $^2J_{HH}$(C-α)
	Eu(DPM)$_3$			
0	−13.72	−14.02	*d*	−17.70
0.125	−13.92	−14.06	−13.11	−17.86
0.250	−13.84	−14.14	−13.38	−18.11
0.375	−14.10	*d*	*d*	−18.24
0.500	−14.04	*d*	−13.61	−18.51
0.750	−14.13	−14.03	−14.05	−18.84
1.000	−14.38	−14.09	−13.98	−18.96
	Eu(FOD)$_3$			
0	−13.72	−14.02	*d*	−17.70
0.125	−14.01	−14.14	−13.55	−18.22
0.250	−14.12	−14.22	−13.74	−18.54
0.500	−14.32	−14.33	−14.07	−19.02
0.750	−14.70	*d*	−14.26	−19.64
1.000	−14.89	*d*	−14.53	−19.70
1.250	*c*	*d*	*c*	−19.88
1.500	−14.79	*d*	−14.52	−19.68
2.000	−14.72	−13.93	−14.44	*c*
2.500	−14.25	−14.23	−14.50	*c*

[a] Assumed to be negative. Values are accurate to ±0.05 Hz or better. [b] Molar equivalent ratio of LSR to substrate (*vide infra*). $\rho \leq 2.5$, since at higher values, peaks were too broad to get reliable values of J. [c] Not measured. [d] Resonances obscured by other peaks or AB pattern coalesced.

known from X-ray diffraction[5] and also since it is a compound being used by the authors as a model for applications of LSR's to conformational analysis. The second substrate chosen was camphor (II) since the rigidity of this latter ketone provides a case precluding the possibility that observed changes in proton spin–spin coupling constants in I might be caused by lanthanide-induced changes in the conformation of its flattened cyclohexanone ring.

In Figure 1 are plotted the magnitudes of the geminal methylene couplings of I and the geminal methylene coupling of the protons α to the carbonyl function of II *vs.* the molar equivalent ratio, ρ, of LSR to substrate ($= L_0/S_0$, where these are the total molar concentrations of LSR and substrate, respectively). The values of the couplings are given in Table I. In all these measurements, the concentration of substrate was kept constant at 0.15 M.

The couplings vary linearly with the observed incremental shifts in all cases studied and, in using LSR's to extract values of coupling constants, the best procedure to follow is to perform a regression analysis between these two parameters. However, the couplings were also linear with ρ for values of the latter less than ∼0.7 (see straight lines in the plots) and such plots are presented here to make clear the concentration dependence of the couplings.

Lewis acid (the LSR) binding with the substrate. That the effects observed are primarily substituent effects rather than conformational changes induced by the LSR is well borne out by the results for camphor and by the fact that the relative changes in observed shifts at the same ρ values are much less than those of the couplings. (If this were not primarily a substituent effect, the applicability of LSR's to the study of molecular structure in solution would be seriously jeopardized.) Of course, some perturbation in the relative populations of conformers for compounds which interconvert readily may be expected and such a case has been reported for a multifunctional substrate.[7] However, only substituent effects, and not geometrical changes, can be expected to be the main contributor to the observed coupling constant changes of a very great number of interesting molecules.

(6) *E.g.,* A. M. White and G. A. Olah, *J. Amer. Chem. Soc.*, **91**, 2943 (1969).
(7) J. F. Caputo and A. R. Martin, *Tetrahedron Lett.*, 4547 (1971).
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previously reported syntheses (B. L. Shapiro, *et al., Tetrahedron Lett.*, 223 (1971)) and was fully characterized by analysis, properties, and derivatives, as well as by X-ray crystallographic studies (see ref 5).
(5) R. L. R. Towns and B. L. Shapiro, *Cryst. Struct. Commun.*, **1**, 151 (1972).