controlled interaction with a nucleophilic substrate. Instead, the electrophilicity of the activated oxygen appears to be covalently controlled. Low energy orbitals which are not completely occupied and yet contain considerable electron density on the oxygen atom can serve as primary electron acceptors in covalent interaction leading to the transfer of the oxygen to a nucleophilic substrate. In previous studies, similar low-lying, oxygen containing orbitals were found to be present in chemical models of cytochrome P-450 such as peroxytrifluoroacetic acid[23] and chromyl chloride.[24] A unifying picture of the electronic nature of the electrophilic oxygen in these systems based on covalent rather than charge controlled substrate interaction thus appears to be emerging from these studies.

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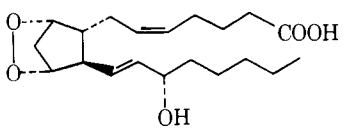
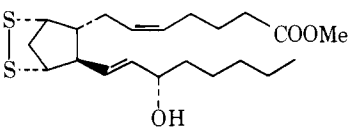
Simple Synthesis of Methyl (5*Z*,9α,11α,13*E*,15*S*)-9,11-Epidithio-15-hydroxyprosta-5,13-dienoate, Endodisulfide Analogue of PGH_2

Sir:

The outstanding biological activity of prostaglandins has stimulated numerous investigations of chemical modifications of the prostanoid structure.[1] Recently, there has been an active interest in the variations of the endoperoxide ring systems of PGG_2 and PGH_2 which possess an interesting spectrum of biological activity.[2] Because of their fairly short half-life in aqueous buffer, the design and synthesis of a stable and active analogue were deemed important.[3] The endodisulfide analogue of PGH_2, methyl (5*Z*,9α,11α,13*E*,15*S*)-9,11-epidithio-15-hydroxyprosta-5,13-dienoate (**1**), is of special interest, since a dithio linkage is more stable chemically than a peroxide unit and the molecular geometry of the rigid endodisulfide ring system approximates that of PGH_2. Herein we report a new and highly effective synthetic approach to **1** and also some biological effects of this readily accessible, stable PGH_2 analogue.

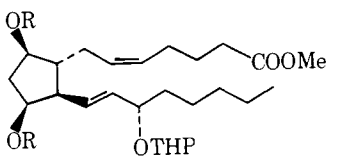


PGH_2

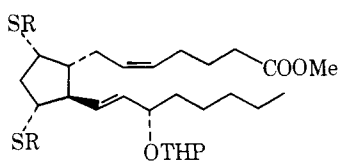


1

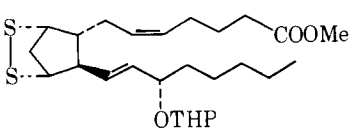
To construct the endodisulfide ring of structure **1**, we required a suitably stereochemically functionalized prostaglandin derivative. For this purpose, we chose dimesylate monotetrahydropyranyl ether **2**, which was obtained by reaction of 9β,11β-diol **3**[4] with mesyl chloride (2.2 equiv) and triethylamine (4 equiv) in methylene chloride at −20 °C for 1 h in 91% yield.[3b] Treatment of dimesylate **2** with excess sodium thioacetate in dimethyl sulfoxide–*N*,*N*-dimethylformamide (1:1) at 50 °C for 20 h afforded the dithio acetate, **4** (60% yield), which was saponified quantitatively with potassium carbonate in methanol at 25 °C for 30 min to provide 9α,11α-dimercapto



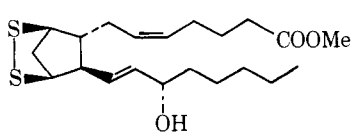
2, R = Mes
3, R = H



4, R = Ac
5, R = H



6



7

derivative **5** in pure form after column chromatography on silica gel; IR (liquid film) 2560 cm^{-1} (SH). The endodisulfide unit in **6** could be prepared under carefully chosen conditions which precluded further oxidation and other side reactions.[5] Specifically, upon treatment of **5** with 1.5 equiv of active manganese dioxide in degassed toluene at −20 °C for 40 min under argon,[6] **6** was formed along with minimal side products, and could be isolated in 86% yield after column chromatography on silica gel using cyclohexane–ethyl acetate (4:1) as eluent. Removal of the tetrahydropyranyl ether from disulfide **6** (acetic acid–water–tetrahydrofuran, 12:3:2) at 40 °C for 1 h afforded the disulfide analogue of PGH_2 (**1**) in 49% isolated yield; $[\alpha]^{18}_D$ +3.6° (*c* 0.6, chloroform).[7] The structural assignment follows from (a) the mass spectrum (molecular ion at *m/e* 398.1959, calcd 398.1949); (b) the IR spectrum; and (c) a negative Ellman test[8] on TLC assay.[9]

Further support regarding the stereochemistry of product **1** was obtained by the chemical synthesis of the 9,11-epimer of **1.** Thus, starting from the 15-tetrahydropyranyl ether of $PGF_{2\alpha}$ methyl ester[10] and using the same procedure used for the sequence, **2** to **1,** there was produced 9β,11β-dithio analogue **7.** Although disulfides **1** and **7** are spectroscopically indistinguishable (IR and NMR), the thin layer chromatographic behavior of **7** on silica gel using cyclohexane–ethyl acetate as eluent is different from that of compound **1:** R_f 0.35 for **1** and 0.33 for **7.** In addition, **1** was very active biologically as an endoperoxide mimic whereas the epimer, **7,** was not.

Like the endoperoxides, cyclic sulfide **1** is very effective in contracting the aorta strips.[11] Thus, analogue **1** was 24 times more active than PGH_2 and 5000 times more active than PGE_2 in this assay. Endodisulfide **1** also caused marked, rapid and irreversible aggregation of platelets washed in Tyrodes solution.[12] Further study of the biological activity of **1** is in progress.[13]

The simple and effective synthesis of endodisulfide **1** described above makes available a biologically active member of the PGH_2 analogue series which, in contrast to the highly labile PGH_2, does not undergo facile decomposition chemically[14] and may not be rapidly metabolized in vivo.[15]

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(13) Endodisulfides **1** and **7** did not inhibit the formation of PGH_2, whereas, 9α,11α-dimercapto $PGF_{2\alpha}$ methyl ester, readily available by deprotection of compound **5,** specifically inhibited PGH_2 biosynthesis. These results will be published elsewhere.
(14) Analogue **1** was stable in cyclhexane–ethyl acetate in the presence of Kiesel gel for at least 5 days.
(15) Biological degradation of cyclic disulfide **1** in vivo is under investigation.

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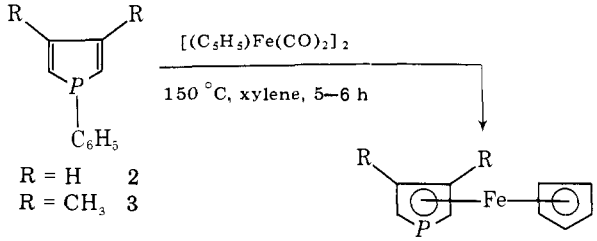
Phosphaferrocene

Sir:

Recently Braye and Joshi[1] have described an attempted synthesis of a tetraphenyl-substituted phosphaferrocene by reaction of potassium 2,3,4,5-tetraphenylphospholyl with cyclopentadienyldicarbonyliron iodide. The $CpFe(CO)_2L$ σ complex thus formed (L = phospholyl) was stable and did not lose CO upon heating to give the expected phosphaferrocene. This stands in sharp contrast to observations when L = pyrrolyl (see the synthesis of azaferrocene[2]). In view of our recent success in the synthesis of phosphacymantrenes,[3] we thought that the failure of Braye and Joshi was not due to an intrinsic instability of the phosphaferrocene system but, more probably, to the high electron-withdrawing ability of the tetraphenyl substitution which destabilized the desired π-aromatic complex. Since the synthesis of phospholyl anions[4] does not give very satisfactory results with the less substituted *P*-phenylphospholes, we studied the reaction of these phospholes with dicyclopentadienyltetracarbonyldiiron, **1.** We expected a cleavage of the P-phenyl bond of *P*-phenylphospholes in the same way as with decacarbonyldimanganese.[3] Indeed, reactions of an equimolecular amount of **1** in boiling xylene at 150 °C with the phospholes **2** and **3**[5] afford, inter alia, the expected phosphaferrocenes **4** and **5,** respectively.



4 yield ~30% mp ~152 °C dec
5 ~20% 78 °C

Both phosphaferrocenes are orange solids which appear to be less stable than the corresponding phosphacymantrenes. They are recovered from the reaction mixture by column chromatography (silica gel 60 merck, 70–230 mesh). They form an orange band which is eluted first by a benzene–hexane mixture (20–80).[6]

We give hereafter their ^1H NMR and mass spectral data. Other data (analytical, IR, and ^{13}C and ^{31}P NMR) will be reported elsewhere. ^1H NMR (60 MHZ, $CDCl_3$, internal Me_4Si): **4** δ 4.03 (d of m, J_{H-P} = 38 Hz, Hα), 4.35 (s, C_5H_5),