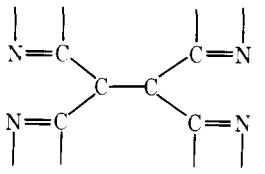

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plexes bear some similarities to quinone–hydroquinone couples and have the potential of functioning as multiequivalent redox reagents. The nickel(II) and copper(II) complexes of $Me_2[14]1,11$-dieneN$_4$ are also easily oxidized and the locus of oxidation in these complexes is being investigated.[16,17]

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(1) Partial support of this research by the National Institutes of Health (AM 14341) is gratefully acknowledged.
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(11) Ligand abbreviations are based on conventions reviewed and summarized by Melson:[12] $Me_2[14]1,11$-dieneN$_4$ = 12,14-dimethyl-1,4,8,11-tetraazacyclotetradeca-1,11-diene; $Me_2[14]1,11$-dieno(−1)N$_4$ = 12,14-dimethyl-1,4,8,11-tetraazacyclotetradeca-1,11-dieno(−1); $Me_2[13]1,10$-dieneN$_4$ = 11,13-dimethyl-1,4,8,11-tetraazacyclotrideca-1,10-diene; $Me_2[13]1,10$-dieno(−1)N$_4$ = 11,13-dimethyl-1,4,8,11-tetraazacyclotrideca-1,10-dieno(−1); [14]aneN$_4$ = 1,4,8,11-tetraazacyclotetradecane; $Me_6[14]4,11$-dieneN$_4$ = 5,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene; $Me_4[14]$tetraeneN$_4$ = 2,3,9,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene; phen = 1,10-phenanthroline.
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(14) As a matter of convenience, we have investigated the electrochemistry of the organic ligand mostly in the aprotic medium. The dimeric species are also electroactive, but the electrochemistry is complicated by further irreversible ligand oxidation, coupled to protic equilibria. For the cobalt(III)–(II) couple of 13,13'-bis[Co($Me_2[14]1,11$-dieneN$_4$)(OH$_2$)$_2$]$^{6+}$ we estimate $E_{1/2} \simeq 0.42$ V vs. NHE.
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(16) Khalifa, M. A.; Endicott, J. F., work in progress. In our hands the previously described[15] "preparation" of the nickel(II) dimer has been very inefficient (yields of less than a few percent); some of the oxidation products may involve ligand dehydrogenation as reported by Busch and co-workers.[17] Such aerial oxidations of β-diiminato complexes may also be complicated by ligand oxygenation. Our preliminary work, as well as the work of others cited above, suggests that the chemistry of these systems couples the properties of metal and ligand in ways that are not always well understood.
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Jay A. Switzer, John F. Endicott*
Department of Chemistry, Wayne State University
Detroit, Michigan 48202
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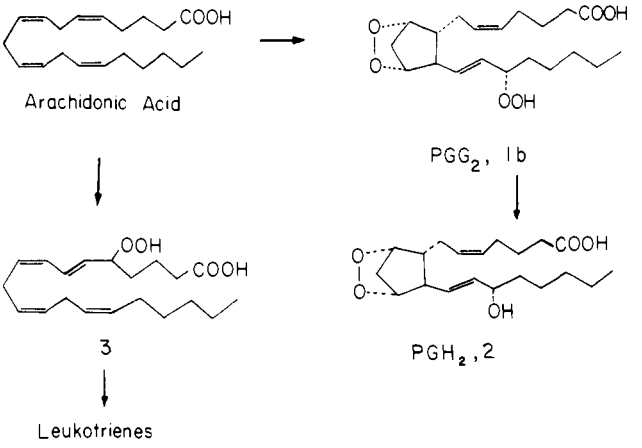
Prostaglandin G_2

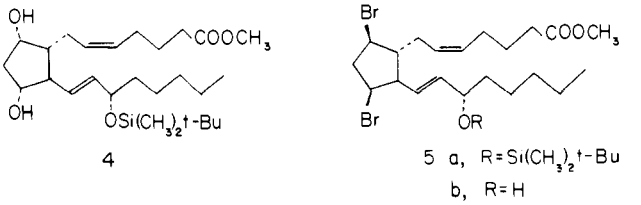
Sir:

The finding that compounds containing the peroxide group are important natural products derived from polyunsaturated fatty acids has resulted in a renewed interest in peroxide synthesis.[1-5] Several methods[1-4] have been developed for the construction of the bicyclo[2.2.1] endoperoxide nucleus of PGH_2 (**2**), and syntheses of this compound[6] and its methyl ester[3,7] have been recently reported. The allyl-type hydroperoxide group is also the focus of considerable chemical interest since this functionality is present in a proposed biological intermediate (**3**) to the slow reacting substance of anaphylaxis (SRS-A) as well as in PGG_2 (**1b**).



PGG_2 is the first isolable intermediate formed in the conversion of arachidonic acid into the prostaglandins and thromboxanes and, as such, it plays a central role in the biochemistry of fatty acids. It is difficult to obtain pure from biological sources and the lability of the 9,11-peroxide linkage and the 15-hydroperoxide group pose a dual threat in any synthetic approach to the compound. In fact, no reports of attempted syntheses of PGG_2 have appeared in the literature. The reaction of alkyl halides with hydrogen peroxide and silver trifluoroacetate[9,10] has proven to be a method suitable for the generation of the 9,11-peroxide bridge of PGH_2 (**2**),[6,7] and it occurred to us that this method might also be used to introduce the allylic 15-hydroperoxy group of PGG_2.[11] We report here the first chemical synthesis of PGG_2. In this synthesis, the 9,11-peroxide bridge and the 15-OOH are simultaneously introduced via the silver trifluoroacetate/hydrogen peroxide method in a triple displacement reaction.

The synthesis proceeds from $PGF_{2\alpha}$ methyl ester through the 15-*tert*-butyldimethylsilyl ether[3] (**4**) to **5a**. The crucial 9β,11β-dibromo derivative (**5b**) was previously prepared[3,6] by



displacement of 9α,11α-disulfonates with bromide ion. This approach has been criticized[12] because the bromide displacement reaction leads to a mixture of epimeric dibromides and the desired isomer is isolated in only 20% yield after a tedious chromatographic purification. The intermediate **5a** may be prepared in one step from **4** (50% yield) by treatment of **4** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate[13] and tetraethylammonium bromide. No epimers of **5a** are formed by the use of these extremely mild reaction conditions and the preparation of **5** by this route gains not only in terms of overall yield (the sequence **4** → **5b** is shortened by one step and the yield is higher) but also in that the difficult chromatographic separation of isomers is avoided. Thus, 0.1265 g of **4** was treated with 0.9276 g of 2-chloro-3-ethylbenzoxazolium tetrafluoroborate and 1.3854 g of tetraethylammonium bromide in 7 mL of methylene chloride at −15 °C for 20 min. Following an aqueous wash and chromatography on silica with 2% acetone–98% hexane, 0.080 g of pure **5a** was isolated. Hydrolysis

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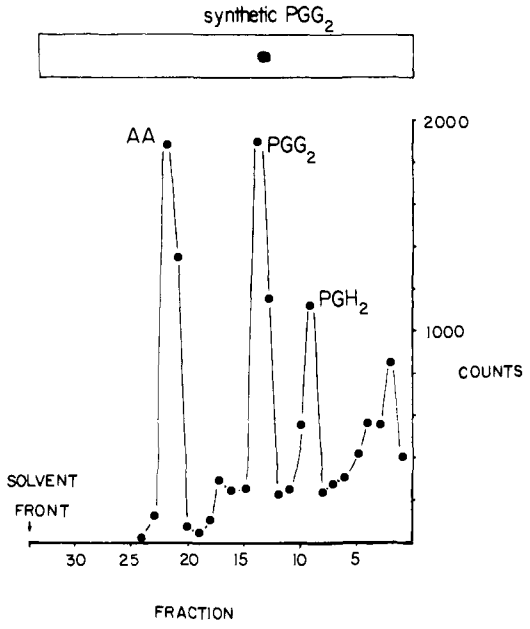
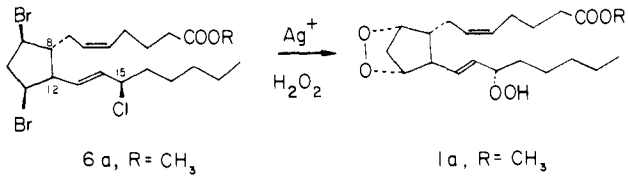


Figure 1. Radioactivity thin layer chromatograms of prostaglandin products obtained from arachidonic acid and ram seminal vesicle microsomes (below). Thin layer chromatogram of synthetic PGG_2 (above).

of **5a** to **5b** proceeded[6] in 86% yield. **5b** prepared in this way may be converted into PGH_2 by published procedures[6,7] and the use of the Mukaiyama reagent[13] improves the overall yield of $PGF_{2\alpha} \rightarrow PGH_2$ from 2.3 to 7.0%.

Reaction of **5b** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate and benzyltributylammonium chloride provides **6a** in an 82% isolated yield.[14] The structure of **6a** is supported by elemental analysis and ^{13}C and ^{1}H NMR spectra. A comparison of the ^{13}C spectra of **5b** and **6a** is particularly informative and suggests that the conversion of **5b** into **6a** occurs cleanly by substitution at C-15 with no C-13-substituted S_N2' product being formed in the reaction. Thus, in going from **5b** to **6a**, the C-15 resonance is shifted, as expected,[15] some 9 ppm upfield (δ 72.6 to 62.5) and C-16 is shifted downfield[15] nearly 2 ppm (δ 37.0 to 38.7). On the other hand, the chemical shifts of C-8 and C-12 are unaffected by the substitution, a result that is expected for substitution at C-15 but one that would not be anticipated had an S_N2' displacement at C-13 occurred. It is not surprising that S_N2' substitution is not observed since approach to C-13 would appear to be severely hindered by the β bromides at C-9 and C-11. Hydrolysis of the methyl ester of **6a** could be effected with commercial hog pancrease lipase, a method that was previously described[6] for the hydrolysis of **5b**.



6a, R = CH_3
b, R = H

1a, R = CH_3
b, R = H

PGG_2 (**1b**) is formed from **6b** in one step. Treatment of 3 mg of **6b** in 0.5 mL of ether with 91 mg of silver trifluoroacetate and 90 μL of 90% hydrogen peroxide leads to PGG_2 in an estimated (vide infra) 15–20% yield.[16] PGG_2 is purified by high pressure liquid chromatography (LC) at −5 °C on 10 μ silica. It is less stable on LC than PGH_2 (room temperature LC of PGG_2 was unsuccessful) and it is appreciably less polar than PGH_2 as expected.[8] PGG_2 chromatographs with a retention volume of 27 mL with 20:80 ethyl acetate–hexane whereas PGH_2[6] had a significantly longer retention volume.[17] Synthetic PGG_2 cochromatographs on TLC with the biologically prepared compound (Figure 1) and it is converted into $PGF_{2\alpha}$ by reaction with triphenylphosphine.[18] $PGF_{2\alpha}$, thus prepared, was converted into its tris(trimethylsiloxy)methyl ester and GC–MS analysis confirmed its structure.

Synthetic PGG_2 aggregates indomethacin-treated platelet-rich plasma[19] and contracts rabbit aorta strip. The rabbit aorta contraction is enhanced by prior incubation of PGG_2 with platelets.[20] Treatment of synthetic PGG_2 with ram seminal vesicle microsomes and reduced glutathione converts it into PGE_2[21] as assayed by a rat stomach fundus strip.[22] On the basis of these quantitative biological assays, we estimate that the yield of **1b** formed from **6b** in the triple displacement reaction is 15–20%.

The synthesis of PGG_2 reported here rests on the versatility of the Mukaiyama alkyl halide synthesis[13] and the silver/hydrogen peroxide method[5-7,9,10] of peroxide synthesis. A variety of lipid peroxide and hydroperoxide compounds of biological interest such as **3** and analogues of PGG_2 and PGH_2 would appear to be available by chemical synthesis.

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(17) A Waters Microporasil analytical column was jacketed so that an ethylene glycol–water solution could be circulated for cooling.
(18) Several solvents were used to compare $PGF_{2\alpha}$ or its methyl ester with the product of triphenylphosphine reduction of PGG_2; see ref 3. These analyses show the absence of the C-15 $PGF_{2\alpha}$ epimer and indicate the stereochemical purity of synthetic PGG_2.
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(23) Paul M. Gross Chemical Laboratory.
(24) National Institutes of Environmental Health Sciences.

Ned A. Porter,*[23] Jim D. Byers,[23] A. E. Ali[24] Thomas E. Eling[24]

Paul M. Gross Chemical Laboratories, Duke University Durham, North Carolina 27706 and the National Institutes of Environmental Health Sciences Research Triangle Park, North Carolina 27709

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