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AN ELECTRON TRANSFER MODEL FOR PGI BIOSYNTHESIS

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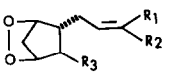
A biomimetic conversion of the endoperoxide 1b to prostacyclin (PGI_2) analogs is achieved with the aid of ferrous ion catalysis.

Sir:

Several mechanisms have been suggested for the biosynthesis of PGI_2 (2a) from PGH_2 (1a)(1-5) but little experimental evidence bearing directly on the question of mechanism has been presented. Studies designed to mimic the enzymatic conversion of PGH_2 to PGI_2 have been limited by the quantity of PGH_2 available and also by the complexity of product



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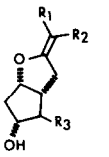
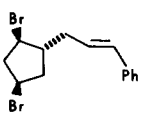


2

a $R_1 = (CH_2)_3COOH$, $R_2 = H$, $R_3 = CH=CH-CHOH-C_5H_{11}$ b $R_1 = H$, $R_2 = Ph$, $R_3 = H$

mixtures generally obtained. We chose the simple system (1b) for studies of this conversion since (a) we could prepare this compound in 100 mg quantities by chemical synthesis and, (b) we anticipated that the removal of the R_3 substituent on the endoperoxide nucleus would potentially simplify the product mixtures obtained in biomimetic studies. We report here on the reaction of (1) with one electron reducing agents such as Fe(2+). Our results support the notion that conversion of the PGH_2 endoperoxide nucleus to the PGI_2 structure may be catalyzed by an electron transfer shuttle mechanism.



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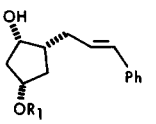
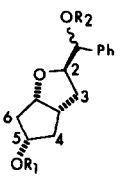


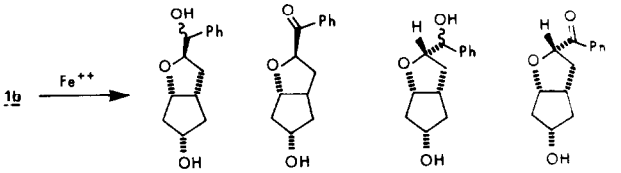
4 a R = H
b R = THP



5 a $R_1 = R_2 = H$
b $R_1 = R_2 = Ac$
c $R_1 = THP$, $R_2 = Ac$

The endoperoxide (1b) was prepared in 45% yield by reaction of the dibromide (3) with hydrogen peroxide/silver trifluoroacetate as previously described for synthesis of PGH_2.(6) The dibromide (3) was prepared from the diol (4a) by reaction with triphenylphosphine dibromide. A seven step synthesis starting from cyclopentadiene and α-chloroacrylonitrile patterned after Corey's synthesis(7) of $PGF_{2\alpha}$ provided (4a).

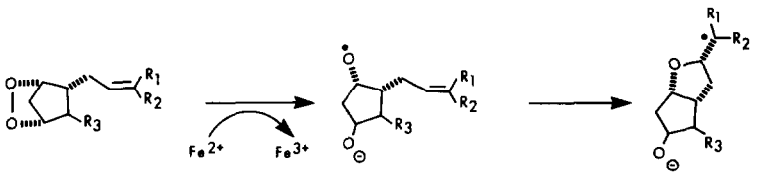
Reaction of (1b) in acetonitrile/water with $FeSO_4$ for 30 min at 0° led to complete consumption of endoperoxide.(8) The reaction mixture was chromatographed on a Partisil PAC-10 (Whatman) column with 4% isopropanol/hexane solvent and the structures of products isolated were determined by spectroscopy and independent synthesis. Product distributions obtained from a typical experiment were: (5a) trace amounts; (6) 3%; (7) 34%; and (8) 11%. The distribution of products does not depend on whether the reaction is carried out



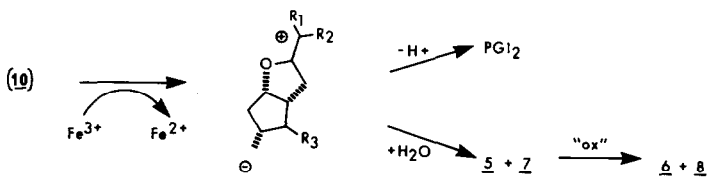
under oxygen or nitrogen. Other less polar products were also isolated (3-5%) in the (1b)/Fe^{++} reaction and these products appear to be epoxy-aldehydes similar to compounds isolated by Salomon in decomposition of the parent [1,2]-dioxabicyclo[2.2.1]heptane.(9)

The exo derivatives (5a) and (6) could be interconverted by oxidation with MnO_2 and reduction with lithium aluminum hydride and the endo phenone (8) could be reduced to the two epimeric endo alcohols (7). Independent synthesis of the exo isomers was achieved by reaction of (4b) with lead tetraacetate. Thus, reaction of (4b) with lead tetraacetate in refluxing benzene gave two exo stereoisomers of (5c) and the derivatives of these stereoisomers (5a) and (5b) could be obtained by appropriate derivatization or deprotection. Yield of (5b) formed from (4b) in this three step sequence was 60%. Oxidation of the two stereoisomers (5a) formed in the lead tetraacetate reaction with MnO_2 gave the same phenone (6) indicating that the two diastereomers differ only by configuration (threo/erythro) about C-2 and the benzylic center. Mass spectrometry of the TMS derivatives of (5-8) along with elemental analysis further support the assigned structures. Mass fragments resulting from cleavage of the exocyclic bond at C-2 were the principal ions formed from all of the compounds (5-8). The exo stereochemistry of (5) was estabilised by pmr. An ill-defined quartet at δ 4.48 J = 7Hz for the proton, at C-6a was found for compound (5c). This downfield quartet is observed for over twenty exo stereoisomers of PGI_1(10) and is taken to be diagnostic for exo substitution.(11) Further confirmation of exo substitution of (5) and (6) is provided by the observation that the phenone (8) can be epimerized by base to the less crowded exo isomer (6).

The conversion of (1b) to products having the bicyclo [3.3.0] structure present in PGI_2 is of mechanistic interest. Turner and Herz(4) have proposed a mechanism for PGI_2 biosynthesis that involves electron transfer from peroxide to Fe^{++} followed by free radical reactions of the alkoxy radicals so generated. The conversion described here is best explained by a similar mechanism that is presented in Scheme I. Free radical cyclization(12,13) of the alkoxy radical generated by reduction of (1b) provides the carbon radical (10) that is then oxidized to the cation (11) by Fe^{3+}.(14,15) Loss of an α proton would give the PGI_2 structure for (1a) but in the medium of this reaction, aqueous acetonitrile, entrapment of (11) by water leads to the isolated products (5) and (7). Oxidation of the labile benzyl alcohols under the conditions of the reaction accounts for formation of the phenones (6) and (8).



(9) (10)



(11)

The stereochemical bias of the lead tetraacetate cyclizations and the endoperoxide/Fe^{2+} reaction require comment. The mechanism of lead tetraacetate catalyzed alcohol cyclizations has been the subject of considerable debate.(16,17) Recent evidence(16) suggests that cyclizations carried out in nonpolar solvents involve a Pb(IV)-alkoxide-π-complex with the target double bond. In the cyclization of (4b), we suggest that such a complex would preferentially give products with exo stereochemistry due to the less crowded nature of the exo π-complex transition state. The stereochemistry of the Fe^{2+} catalyzed cyclization of the endoperoxide provides an interesting contrast to the lead tetraacetate cyclization. The radical intermediate (9) proposed in Scheme I cyclizes with a dramatic endo preference and the cause of this stereoselectivity is not readily apparent. It should be mentioned, however, that the alkoxide of (9) would surely be complexed with ferric ion and models suggest that intramolecular interaction of the metal and the styryl π system is best accommodated by a conformation close to that required for an endo cyclization. We thus suggest that even a weak metal-styryl interaction would tip the exo-endo balance toward the endo isomers.

The conversion of endoperoxide (1b) to the prostacyclin backbone is the first report of such a non-enzymatic conversion and serves to support the Turner and Herz biosynthesis proposal. Attempts to catalyze the conversion of (1b) to prostacyclin with Cu^{2+}, a good peroxide Lewis acid catalyst(18) have failed and the possibility of utilizing other electrophilic catalysts for the conversion is currently being explored.

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