An Electron Transfer Model for Thromboxane Biosynthesis

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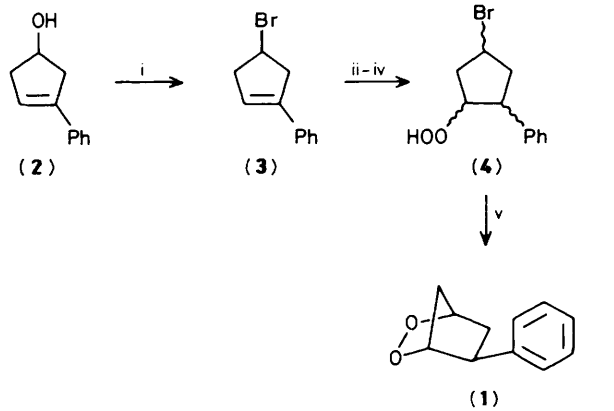
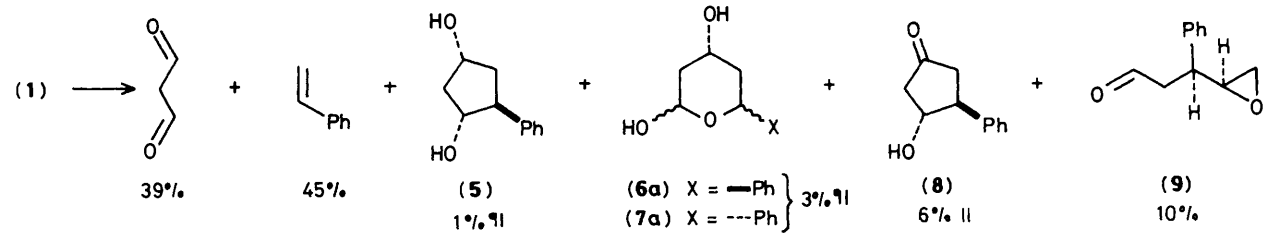
Conversion of prostaglandin endoperoxide model compound (**1**) into the thromboxane B ring system (**6a**) and (**7a**) was achieved with the aid of the ferrous ion.

Prostaglandin endoperoxide (PGH_2) plays a central role in the cyclo-oxygenase system of arachidonic acid metabolism as a substrate for enzymes producing a variety of prostanoids. Several model reactions[1] have been reported that mimic the processes of the metabolism using endoperoxide model compounds or PGH_2 itself. These have provided evidence for the biosynthetic mechanism. However, no model studies have been reported in which the endoperoxde is converted into the thromboxane (TX) skeleton by chemical means alone.† Previously,[3] we have described the 11,12-secoprostaglandin (PG numbering) cyclization model leading to TX analogues. The model was based on the assumption that the C-13–C-14 double bond of the ω side-chain of PGH_2 would play an important role in the bioconversion of the bicyclic moiety of PGH_2 into that of TXA_2. In accord with this mechanism, we



Scheme 1. *Reagents:* i, PPh_3, CBr_4–CH_2Cl_2(70%); ii, BH_3–tetrahydrofuran (THF); iii, O_2; iv, H_2O_2 (35%, 3 steps); v, Ag_2O–CH_2Cl_2 (58%).

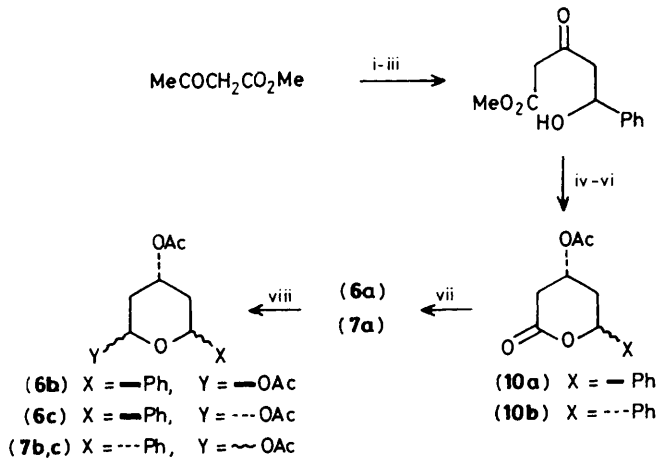
† Treatment of PGH_2 with hemin in aqueous buffer was shown to give TXB_2 by radiochemical methods.[2]



Scheme 2

now present the first model reaction in which the endoperoxide is converted into the TXB ring system. A simplified endoperoxide model, 5-*exo*-phenyl-2,3-dioxabicyclo[2.2.1]heptane (**1**), was chosen in which the ω side-chain is substituted by a phenyl group to act as the C-13–C-14 double bond equivalent and the α side-chain is removed.

The model compound (**1**) was prepared from 3-phenylcyclopent-3-en-1-ol (**2**)[4] as shown in Scheme 1. Hydroperoxide stereoisomers (**4**) were prepared in modest yield by hydroboration of (**3**) followed by sequential oxidation with oxygen and hydrogen peroxide.[5] The hydroperoxides (**4**) were then converted into crystalline endoperoxide (**1**) using silver oxide.[6] A corresponding 5-*endo*-phenyl isomer of (**1**) was formed only in a trace amount. The structural assignment of (**1**) was based on its spectroscopic data‡ and quantitative reduction into *trans*-2-phenyl-*cis*-4-hydroxycyclopentan-1-ol (**5**) with $SnCl_2$.[7] On treatment of (**1**) with $FeSO_4$ (2 equiv.) in aqueous acetonitrile at 0 °C for 30 min, formation of the products illustrated in Scheme 2 was observed. Although the production of malondialdehyde and styrene was the major mode of reaction, the products (**6a**) and (**7a**) bearing a 2,4-dihydroxytetrahydropyran ring, the TXB ring moiety, were found together with primary PG-like products (**5**) and (**8**).§ The products (**6a**) and (**7a**) were isolated as a mixture of their corresponding diacetates (**6b**) and (**7b,c**) after acetylation of the reaction mixture. They were identified by comparison of their spectroscopic data and chromatographic behaviour (t.l.c. and h.p.l.c.) with the authentic compounds, prepared independently as shown in Scheme 3. Stereoisomers of acetoxy-lactone (**10a**) and (**10b**) were prepared from methyl acetoacetate and benzaldehyde by conventional reactions and separately subjected to di-isobutylaluminium hydride reduction to (**6a**) and (**7a**), respectively. Acetylation of (**6a**) thus prepared afforded separable diacetates (**6b**) and (**6c**) in a ratio of 11 : 1.‡ The minor product (**6c**) could not be isolated from the diacetates of the endoperoxide reaction products. However, the prepared (**7a**) was converted into a mixture of diacetates (**7b,c**).‡ The endoperoxide reaction product (**5**) was also isolated as the corresponding diacetate and (**8**) as its dehydrated form, 4-phenylcyclopent-2-en-1-one. Epoxyaldehyde (**9**) was identified by synthesis of the authentic compound.‡ Quantitative analyses of malondialdehyde and styrene were by the thiobarbituric acid test[8] and h.p.l.c., respectively. Other electron transfer reagents such as Ru^{II} or Pd^{0} [1c] in an aqueous solvent failed to yield (**6a**) and (**7a**).



Scheme 3. *Reagents:* i, NaH–THF; ii, Bu^nLi; iii, PhCHO, 0 °C (89%); iv, $NaBH_4$–MeOH; v, LiOH–H_2O–MeOH; vi, Ac_2O [3 steps, 35% into (**10a**) and 35% into (**10b**)]; vii, di-isobutylaluminium hydride–THF–CH_2Cl_2 [28% into (**6a**), 28% into (**7a**)]; viii, Ac_2O–pyridine (*ca.* 100%).

The formation of diol, ketol, epoxyaldehyde, and malondialdehyde (and its fragment, styrene) is interpreted by the well precedented O–O bond cleavage reaction of endoperoxides.[1] A possible pathway leading to the new type of products (**6a**) and (**7a**) is shown in Scheme 4. One-electron transfer from Fe^{II} to the peroxy bond would generate the radical anion (**11**)[1b,d] or the corresponding ferric alkoxide[9] which could undergo radical β-scission[10] resulting in the stabilized benzylic radical species (**12**). This could then be oxidized by Fe^{III} to the carbonium ion (**13**). The TXB-like products (**6a**) and (**7a**) are considered to be formed *via* the benzylic carbonium ion (**13**)

‡ *Physical and spectroscopic data* [n.m.r. (90 MHz) in $CDCl_3$, coupling constants or half-band width (*w*) in Hz, i.r. in $CHCl_3$] of selected compounds: (**1**), m.p. 38—40 °C; ^{1}H n.m.r. δ 1.80—2.70 (m, 4H), 3.30—3.56 (m, 1H), 4.66 and 4.80 (each br. s, each 1H, bridgehead-H), 7.20 (br. s, 5H); mass 176 ($M^{\cdot+}$).

5-*endo*-Phenyl isomer of (**1**), ^{1}H n.m.r. δ 1.90—2.60 (m, 4H), 3.10—3.30 (m, 1H), 4.65 and 4.75 (each br. s, each 1H, bridgehead-H), 7.25 (br. s, 5H).

(**6b**), M.p. 81—82 °C; ^{1}H n.m.r. δ 1.66—2.02 (m, 4H), 2.04 and 2.12 (each s, each 3H), 4.95 (dd, *J* 4, 10, 1H), 5.36 (quintet, *J* 3, 1H), 6.15 (dd, *J* 4, 9, 1H, anomeric-H), 7.32 (br. s, 5H); ν(CO) 1735 cm^{-1}; mass 278 ($M^{\cdot+}$).

(**6c**), ^{1}H N.m.r. δ 1.70—2.45 (m, 4H), 2.08 and 2.14 (each s, each 3H), 5.14—5.35 (m, 2H), 6.25—6.40 (m, $w_{1/2}$ 6, 1H, anomeric-H), 7.35 (br. s, 5H); ν(CO) 1735 cm^{-1}; mass 158 ($M^{\cdot+}$ −2AcOH).

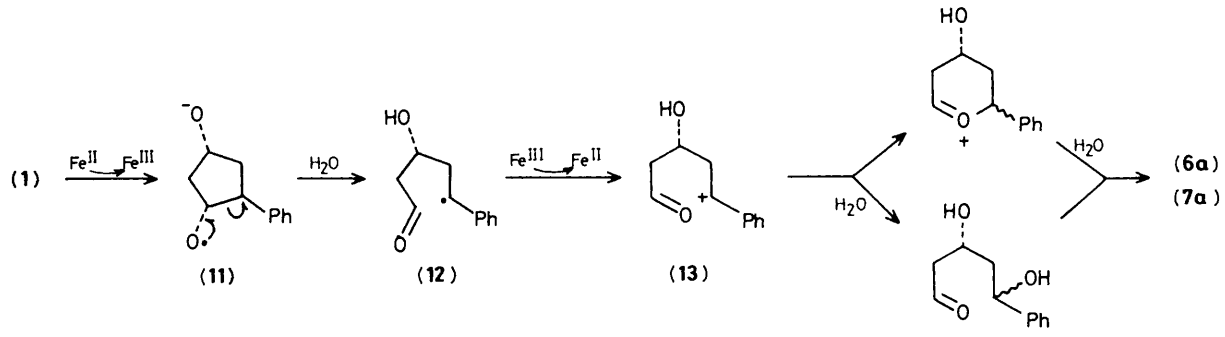
(**7b,c**), ^{1}H N.m.r. δ 1.55—2.45 (m, 4H), 2.02 and 2.10 (each s, each 3H), 4.56 (dd, *J* 2, 12, 0.5 H), 4.96 (dd, *J* 2, 12, 0.5 H), 5.00—5.55 (m, 5.86 (dd, *J* 2, 10, 0.5 H, anomeric-H), 6.40—6.50 (m, $w_{1/2}$ 6, 0.5 H, anomeric-H), 7.32 (br. s, 5H); ν(CO) 1735 cm^{-1}; mass 278 ($M^{\cdot+}$).

(**9**), ^{1}H N.m.r. δ 2.45—2.55 (m, 1H), 2.66—2.90 (m, 3H), 3.06—3.22 (m, 1H), 3.30—3.56 (m, 1H), 7.30 (br. s, 5H), 9.75 (t, *J* 1, 1H, aldehyde); ν(CO) 1715 cm^{-1}; mass 176 ($M^{\cdot+}$).

§ The existence of the products (**5**), (**6a**), (**7a**), and (**8**) in the reaction mixture was confirmed by comparison of t.l.c. and h.p.l.c. data with those of authentic compounds prepared separately [Scheme 3 for (**6a**) and (**7a**)].

¶ The yield of the corresponding diacetate.

‖ The yield of 4-phenylcyclopent-2-en-1-one.



Scheme 4

which corresponds to the 11,12-secoprostaglandin species mentioned previously.[3] The present study supports the hypothesis suggested by Turner and Herz,[11] and may be a clue to understanding the biosynthetic mechanism of TXA_2 formation from PGH_2.

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