

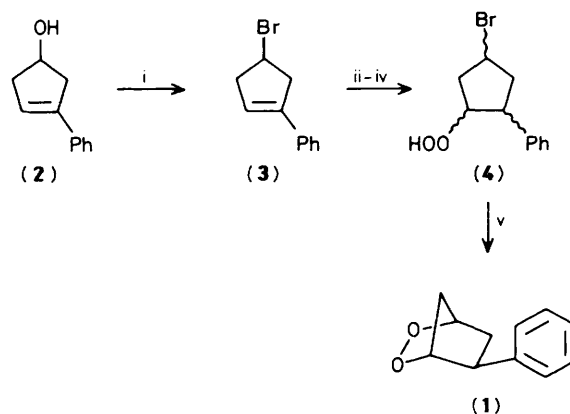
An Electron Transfer Model for Thromboxane Biosynthesis

Kimio Takahashi and Morio Kishi*

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka, 553, Japan

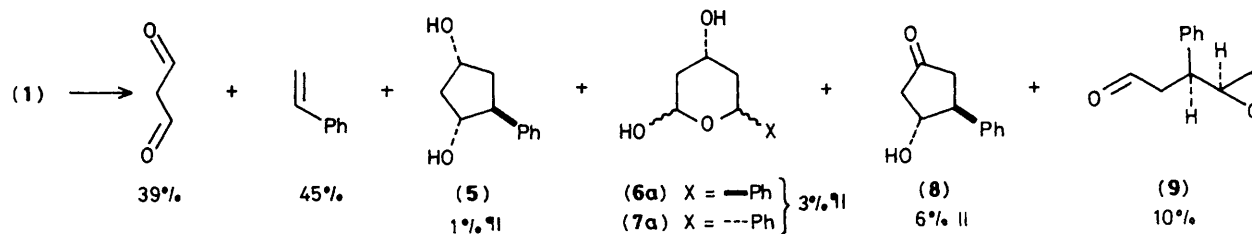
Conversion of prostaglandin endoperoxide model compound (**1**) into the thromboxane B ring system (**6a**) and (**7a**) was achieved with the aid of the ferrous ion.

Prostaglandin endoperoxide (PGH₂) 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 reactions¹ have been reported that mimic the processes of the metabolism using endoperoxide model compounds or PGH₂ itself. These have provided evidence for the biosynthetic mechanism. However, no model studies have been reported in which the endoperoxide 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 PGH₂ would play an important role in the bioconversion of the bicyclic moiety of PGH₂ into that of TXA₂. In accord with this mechanism, we



Scheme 1. Reagents: i, PPh₃, CBr₄-CH₂Cl₂(70%); ii, BH₃-tetrahydrofuran (THF); iii, O₂; iv, H₂O₂ (35%, 3 steps); v, Ag₂O-CH₂Cl₂ (58%).

† Treatment of PGH₂ with hemin in aqueous buffer was shown to give TXB₂ 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-hydroxycyclopent-1-ol (5) with SnCl₂.⁷ On treatment of (1) with FeSO₄ (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

[‡] Physical and spectroscopic data [n.m.r. (90 MHz) in CDCl₃, coupling constants or half-band width (*w*) in Hz, i.r. in CHCl₃] of selected compounds: (1), m.p. 38–40°C; ¹H 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*⁺).

5-*endo*-Phenyl isomer of (1), ¹H 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; ¹H 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*⁺).

(6c), ¹H 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*⁺ - 2AcOH).

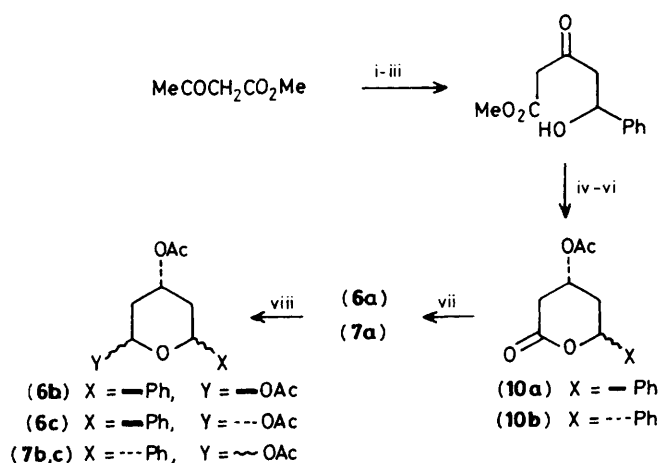
(7b,c), ¹H n.m.r. δ 1.55–2.45 (m, 4H), 2.02 and 2.10 (each s, each 3H), 4.56 (dd, *J* 2, 12, 0.5 H), 4.96 (dd, *J* 2, 12, 0.5 H), 5.00–5.55 (m, 5.86 (dd, *J* 2, 10, 0.5 H, anomeric-H), 6.40–6.50 (m, *w*_{1/2} 6, 0.5 H, anomeric-H), 7.32 (br. s, 5H); ν (CO) 1735 cm⁻¹; mass 278 (*M*⁺).

(9), ¹H 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*⁺).

[§] 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)].

\ddagger The yield of the corresponding diacetate.

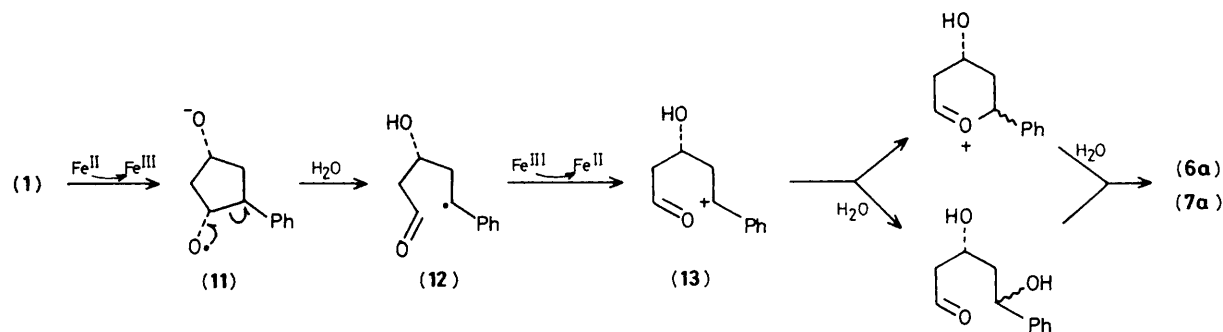
\parallel The yield of 4-phenylcyclopent-2-en-1-one.



Scheme 3. Reagents: i, NaH-THF; ii, BuⁿLi; iii, PhCHO, 0°C (89%); iv, NaBH₄-MeOH; v, LiOH-H₂O-MeOH; vi, Ac₂O [3 steps, 35% into (10a) and 35% into (10b)]; vii, di-isobutylaluminium hydride-THF-CH₂Cl₂ [28% into (6a), 28% into (7a)]; viii, Ac₂O-pyridine (ca. 100%).

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 test⁸ and h.p.l.c., respectively. Other electron transfer reagents such as Ru^{II} or Pd⁰ in an aqueous solvent failed to yield (6a) and (7a).

The formation of diol, ketol, epoxyaldehyde, and malondialdehyde (and its fragment, styrene) is interpreted by the well preceded 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 alkoxide⁹ which could undergo radical β -scission¹⁰ 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)



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 TXA₂ formation from PGH₂.

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