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ELECTROPHILE-INITIATED CONVERSION OF A PROSTAGLANDIN ENDOPEROXIDE MODEL COMPOUND TO THE THROMBOXANE B SKELETON

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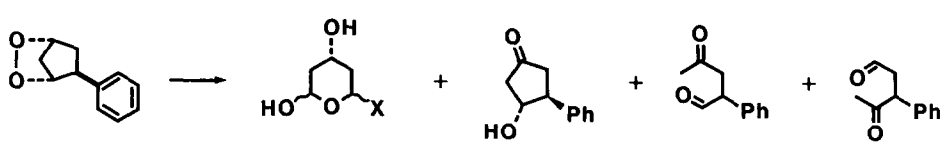
Reaction of the simplified prostaglandin endoperoxide model (**1**) with ferric or cupric ion afforded the lactols (**2a, b**) containing the thromboxane B ring moiety, along with ketol (**3**) and levulinaldehyde derivatives (**4, 5**).

Since the recognition of the central role played by prostaglandin endoperoxide (PGH_2) in the cyclo-oxygenase system of arachidonic acid metabolism,[1] the chemistry of the 2,3-dioxabicyclo[2.2.1]-heptane ring system has attracted much attention.[2] Our interest has been focused on the pathway of thromboxane A_2 (TXA_2) formation from PGH_2 because the biosynthetic mechanism which involves a unique skeletal rearrangement of the bicyclic moiety is still controversial.[3] Recently, we reported the first model reaction in which the simplified PGH model compound (**1**) was converted in low yield to the thromboxane B (TXB) type compounds (**2a, b**) initiated by a one-electron transfer reaction from ferrous ion to (**1**).[4] Of the several hypotheses for TXA_2 biosynthesis from PGH_2,[3] one proposed mechanism involves an initiation of peroxy bond cleavage by electrophilic enzymatic attack on the peroxide oxygen at C-9 (PG numbering) of PGH_2.[3a] This prompted an investigation of the reaction of (**1**) with metal ions which act as Lewis acids toward peroxy compounds.[5] We now describe the efficient conversion of (**1**) into (**2a, b**) via a mechanism different from that previously reported.[4]

On treatment of (**1**) with ferric or cupric salts in aqueous acetonitrile, formation of the products (**2a, b**), (**3**),[4] (**4**)[6] and (**5**), illustrated in Scheme 1, was observed. All the products were identified by comparison with authentic compounds prepared separately.[7] The table lists the reagents tried, the products and their yields. The yield of TXB-like products (**2a, b**) was greatly improved. The formations of ketol (**3**) and levulinaldehyde derivatives (**4**) and (**5**) are precedented in the decomposition reaction of PGH_2 under ionic conditions.[2c] The reactions listed in the table took much more time to complete than that initiated by ferrous ion which was almost instantaneous.[4b] Malondialdehyde (MDA), styrene and (3*S**,4*S**)-4,5-epoxy-3-phenylpentan-1-al, the major products under one-electron transfer conditions,[4] were not formed or only in small amount when formed. It was confirmed in separate experiments that the effect of protons (pH ca. 2-4),[8] generated on hydrolysis of the sulfate and chlorides, on the formation of (**2a, b**) was negligible.[9] In the case of potassium ferricyanate, the



(**1**) (**2a**) X= β-Ph (**2b**) X= α-Ph (**3**) (**4**) (**5**)

Scheme 1

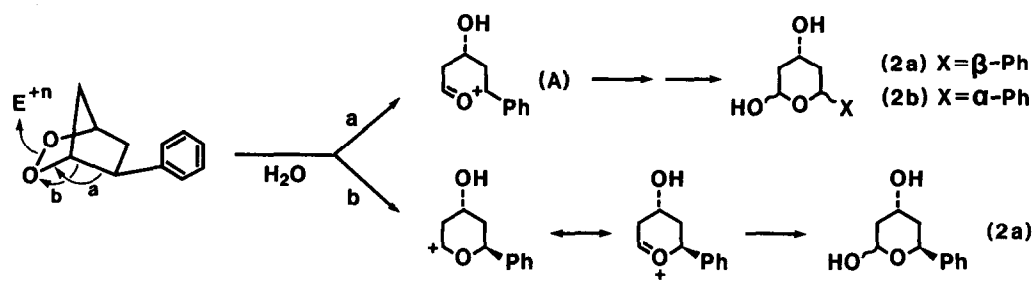
Table. Reaction of (1) with ferric and cupric ions

Reagents[a]	Time (hr)	Products and yields[b] (%) (2a, b)[c]	(3)	(4, 5)[d]
$Fe_2(SO_4)_3$	24	22	39	29
$FeCl_3$	1	20	24	15
$K_3Fe(CN)_6$	24	14	51	20
$CuCl_2$	1	17	35	25

[a] 0.1 M aqueous solution.
[b] Determined by h.p.l.c.
[c] ca. 1:1 mixture at phenyl gorup in each case.
[d] ca. 1:1 mixture in each case.

aqueous solutions are neutral. In aqueous acetonitrile, (1) decomposed very slowly only to give (3), (4) and (5). The findings described above suggest that the ferric and cupric ions contributed to the production of (2a, b).

A possible mechanism of the formation of (2a, b) is described by pathway-a of Scheme 2. The reaction is probably initiated by the coordination of metal ions to one of the peroxide oxygens[5] followed by the heterolytic O-O bond cleavage and the generation of a seco-species, a stable benzylic carbenium ion (A). The formation of both stereoisomers (2a, b) justifies the intervention of (A). The pathway from (A) to (2a, b) was suggested in the previous report.[4] In the aforementioned hypothesis of TXA_2 biosynthesis,[3a] Criegee-type rearrangement[10] (pathway-b of Scheme 2) was proposed after the peroxy bond scission. However, this mechanism does not appear to be operating in the present model system because the mechanism requires retention of configuration at the benzylic carbon.



Scheme 2

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7. The authentic compound of 3-phenyl-levulinaldehyde (**5**) was prepared as follows: 2-phenyl-4-penten-1-al[4b] was allowed to react with MeMgBr and the resulting carbinol was subjected to Swern oxidation to give 3-phenyl-5-hexen-2-one in 70% yield. Treatment of the latter with OsO_4 and $NaIO_4$ afforded (**5**) in 89% yield. $\delta(CDCl_3)$; 9.78 (broad s, 1H), 7.55-7.12 (m, 5H), 4.25 (dd, J = 4, 9 Hz, 1H), 3.45 (dd, J = 9, 18 Hz, 1H), 2.64 (dd, J = 4, 18 Hz, 1H), 2.12 (s, 3H). ν_{max} (neat); 1720 cm^{-1}.
8. "The Merck Index," ed. M. Windholz, Merck & Co., Inc., Rahway, 1983.
9. Under the protic conditions (pH ca. 2-4) (1) afforded slowly (**3**), (**4**) and (**5**), and (**2a, b**) was not detected.
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