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# SYNTHESIS OF THROMBOXANE $B_2$

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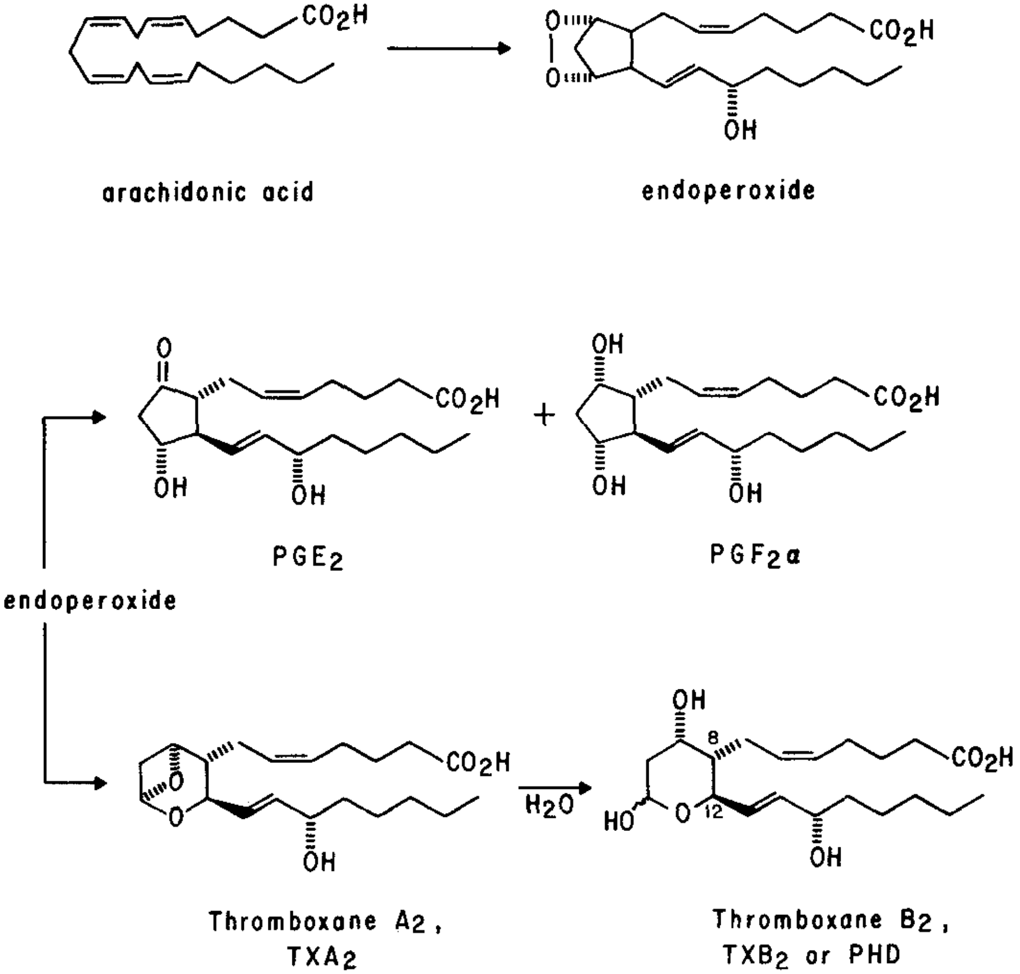
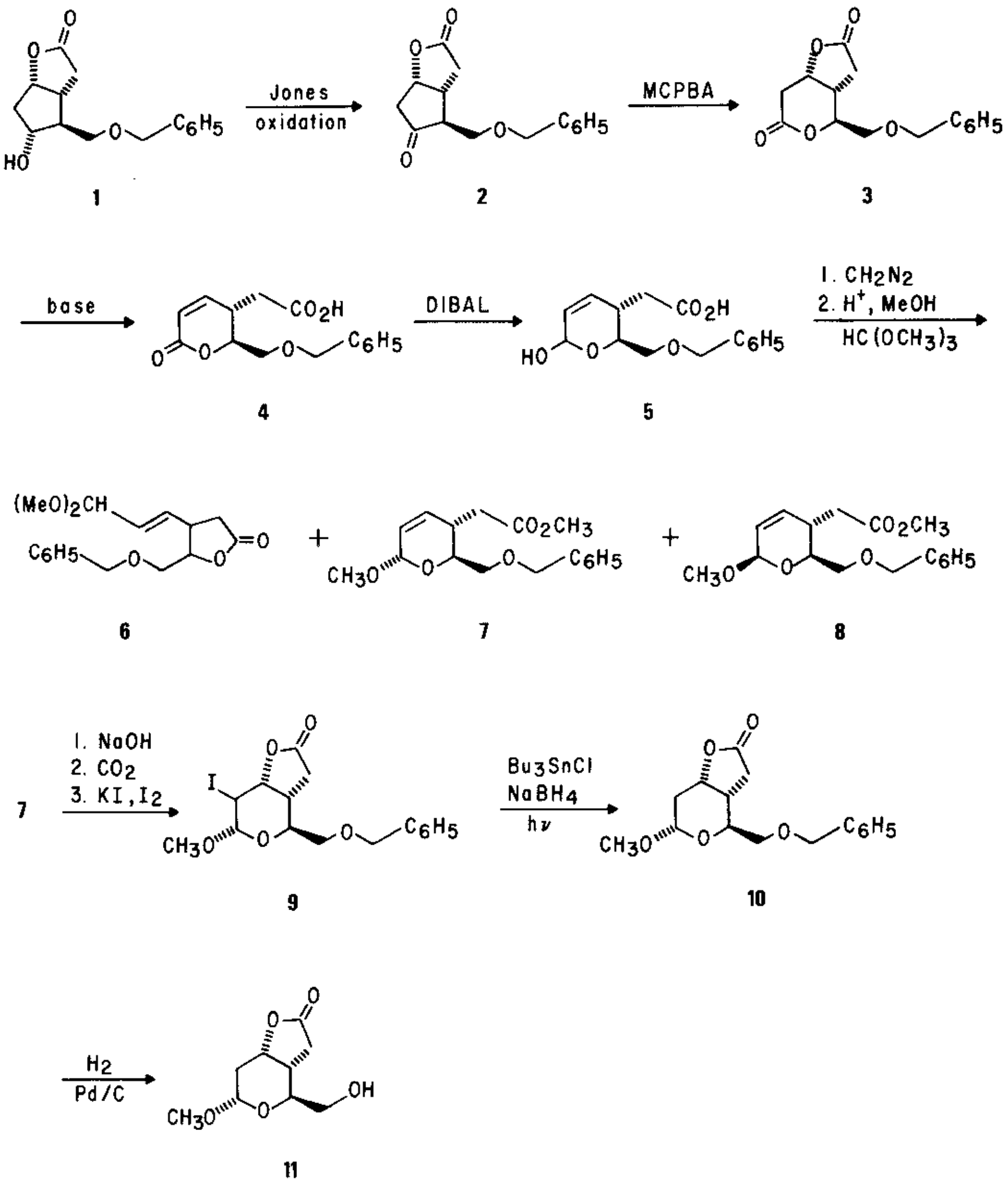
Recently, Hamberg and Samuelsson described a significant new branch in the arachidonic acid metabolism scheme.[1] The endoperoxide which had previously been found to give the prostaglandins (e.g. $PGE_2$ and $PGF_2\alpha$) was found to produce new materials which they called thromboxane $A_2$ ($TXA_2$) and thromboxane $B_2$ ($TXB_2$). On the basis of mass spectral and degradation studies they assign to $TXB_2$ the structure of the hemiacetal of 8-(1-hydroxy-3-oxopropyl)-9, 12L-dihydroxy-5, 10-heptadienoic acid (PHD); that is, the entire structure as represented in Scheme I with the exception of the stereochemistry of the C-12 attached oxygen (prostaglandin numbering). We considered it likely that for the rearrangement of endoperoxide to $TXA_2$ (and thus to $TXB_2$) the stereochemical integrity of C-12 would be maintained. This report in conjunction with the accompanying communication[2] describes a total synthesis of $TXB_2$ in which the conjectured stereochemistry at C-12 is produced stereospecifically.

In the first step of the synthesis, the benzyl alcohol 1[3] was oxidized with Jones reagent to the keto lactone 2. This very base labile compound was treated without purification with m-chloroperbenzoic acid to give the crystalline dilactone 3, mp 108-111° [nmr($CDCl_3$) $\delta$ 2.2-3.4(m,5), 3.68 (d,2,J=4Hz), 4.2-5.15(m,4), 7.28(s,5)][4]. Treatment of 3 with a tertiary amine (e.g. 1,5-diazabicyclo[5.4.0]undec-5-ene) gave the elimination product 4, m.p.65-70° [nmr($CDCl_3$) $\delta$ 2.4-2.7(m,2), 2.7-3.5(m,1), 3.68(d,2,J=4.5Hz), 4.3-4.7(m,3), 5.97(dd,1,J=2,10Hz), 6.80(dd,1,J=3.5,10Hz), 7.28(s,5). Reduction of lactone 4 with DIBAL in toluene at -78° gave the lactol 5 which was directly treated with diazomethane and dry HCl gas in methanol and trimethyl orthoformate. The resultant three products, 6 [nmr($CDCl_3$) $\delta$ 2.3-2.82(m,3), 3.26(s,6), 3.62(d,2,J=3Hz), 4.5(s,2), 4.4-4.8(m,2), 5.3-6.2 (m,2), 7.31(s,5), ir (film) 1780 cm$^{-1}$ (C=O)]; 7 [nmr($CDCl_3$) $\delta$ 1.8-3.2(m,3), 3.42(s,3), 3.65(s,5), 3.6-4.0(m,1), 4.60(d,2,J=2Hz), 4.90(t,1,J=2Hz), 5.6-6.1(m,2), 7.34(s,5); ir (film) 1740 cm$^{-1}$(C=O)];[5] and 8 [nmr($CDCl_3$) $\delta$ 2.0-3.0(m,3), 3.43(s,3), 3.65(s,3), 3.5-4.1(m,3), 4.56(s,2), 4.90(t,1,J=1Hz), 5.6-6.15(m,2), 7.33(s,5); ir (film) 1740 cm$^{-1}$(C=O)] were isolated in 15%, 35% and 3.8% yield, respectively, after chromatographic purification. The ester alkene 7[5] was converted to the crystalline

## SCHEME I


CO2H
arachidonic acid
O
O
CO2H
OH
endoperoxide
endoperoxide
O
CO2H
OH
OH
PGE2
+
OH
CO2H
OH
OH
PGF2α
O
O
CO2H
OH
Thromboxane A2, TXA2
H2O
OH
8
CO2H
HO
O
12
OH
Thromboxane B2, TXB2 or PHD

## SCHEME II


Jones oxidation
MCPBA
base
DIBAL
1. CH2N2
2. H+, MeOH
HC(OCH3)3
1. NaOH
2. CO2
3. KI, I2
Bu3SnCl
NaBH4
hν
H2
Pd/C
C6H5
CO2H
CO2CH3
(MeO)2CH
CH3O
HO
I
OH
1
2
3
4
5
6
7
8
9
10
11

iodolactone 9, m.p. 126-127°, by sequential treatment with N NaOH, $CO_2$, and KI and $I_2$ [nmr($CDCl_3$) $\delta$ 2.2-3.2(m,3), 3.38(s,3), 3.4-4.0(m,3), 4.1-4.4(m,1), 4.5-5.3(m,4), 7.32(s,5); ir (mull) 1780 $cm^{-1}$ (C=O)]. The iodolactone was deiodinated by the method of Corey and Suggs[6] to the crystalline lactone 10, m.p. 80-81° [nmr($CDCl_3$) $\delta$ 2.1-2.9(m,5), 3.32(s,3), 3.5-4.0(m,3), 4.57(s,2), 4.5-5.0(m,2), 7.32(s,5)]. Hydrogenation of 10 over 5% Pd/C in ethanol gave the debenzylated lactone 11 as an oil [nmr($CDCl_3$) $\delta$ 2.0-3.1(m,6), 3.34(s,3), 3.4-3.9(m,3), 4.5-5.0(m,2)]. This alcohol, a single epimer at each chiral center, is identical to the $\alpha$-methoxy isomer of compound 10 in the accompanying communication[2,7] and was transformed into $TXB_2$ as described therein.

## ACKNOWLEDGMENT

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## REFERENCES

1. M. Hamberg and B. Samuelsson, Proc. Nat. Acad. Sci. USA, 72, 2994 (1975).

2. N. A. Nelson and R. W. Jackson, Tetrahedron Lett., XXXX (1976). See also, W.P. Schneider and R. A. Morge, Tetrahedron Lett., XXXX (1976).

3. E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, J. Amer. Chem. Soc., 93, 1490 (1971).

4. The stereochemistry at C-9 (thromboxane numbering) was assigned as shown on the basis of the known retention of configuration in the Bayer-Villiger reaction.

5. The assignment of 7 as the $\alpha$-methoxy anomer could not be made until it was converted to lactones 9 and 10, where the nmr couplings for the anomeric proton were definitive.

6. E. J. Corey and J. W. Suggs, J. Org. Chem., 40, 2554 (1975).

7. The compounds gave identical NMR and IR spectral data and showed identical TLC mobilities on silica gel.