

SYNTHESIS OF THROMBOXANE A₂ ANALOGUE(±)-(9, 11),(11, 12)-DIDEOXA-(9, 11a)-OXA THROMBOXANE A₂

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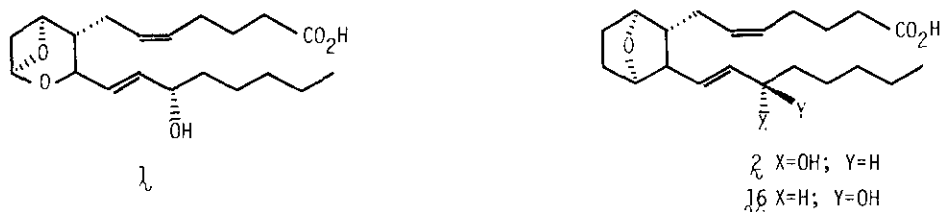
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Summary A synthesis of the thromboxane A₂ analogue, (±)-(9, 11),(11, 12)-dideoxa-(9, 11a)-oxa-thromboxane A₂ (TXA₂) starting from the exo-adduct **3** of maleic anhydride and furan is described.

Thromboxane A₂ (TXA₂) generated by incubation of human blood platelet and the prostaglandin H₂ (PGH₂)^{1,2} is an extremely labile substance with potent blood platelet aggregating and vasoconstrictor properties.^{3,4} Samuelsson et al.¹ assigned its structure to be **1**, on the basis of several trapping experiments and physiological property, although the whole structure of TXA₂ has not yet been confirmed directly. Since TXA₂ possesses an interesting spectrum of biological activity coupled with its lability, synthetic chemists have focussed on obtaining the stable TXA₂ analogues.⁵ Here we wish to report the total synthesis of the stable TXA₂ analogue **2** starting from the exo-adduct **3** of maleic anhydride and furan.

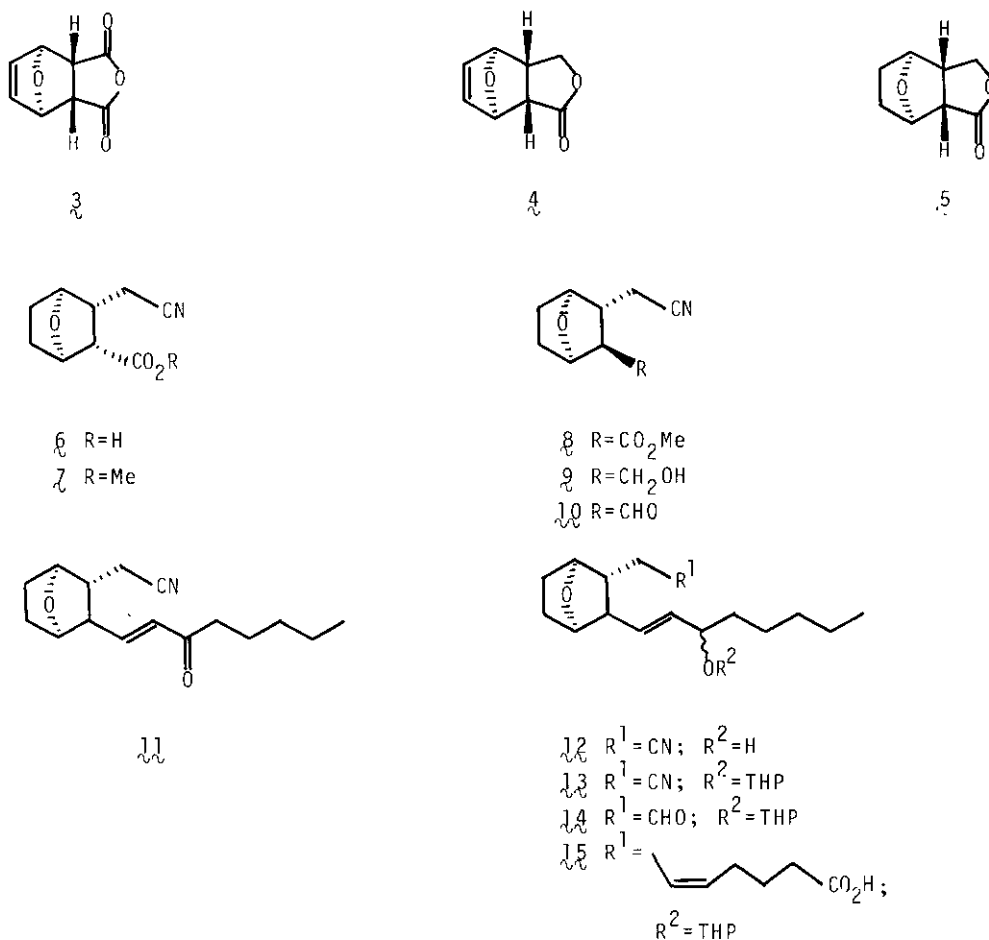
Scheme 1



The first key intermediate **10** was prepared from γ -butyrolactone **4** in 6 steps in 45.7% overall yield. The γ -butyrolactone **4**,⁶ derived from the anhydride **3** by sodium borohydride reduction, was hydrogenated over 5% palladium-carbon in methanol to provide **5**,⁷ mp 115 ~ 117^o [95.3%, ν_{max} 1760

cm^{-1} , m/e 154 (M^+)]. Treatment of $\bar{5}$ with potassium cyanide in dimethyl sulfoxide at 190° for 4.5 h gave the cyanated carboxylic acid $\bar{6}$. Without further purification, the crude carboxylic acid $\bar{6}$ was treated with diazomethane to afford the corresponding α -methyl ester $\bar{7}$, mp $88 \sim 89^\circ$ [62.7 % from $\bar{5}$, ν_{\max} 2260, 1725 cm^{-1} , δ 3.75 (3H, s, OCH_3), m/e 195 (M^+)]. Epimerisation of the α -isomer $\bar{7}$ to the β -isomer $\bar{8}$, mp $65 \sim 67^\circ$ (97.1 %, ν_{\max} 2260, 1725 cm^{-1} , δ 3.66 (3H, s, OCH_3), m/e 195 (M^+)] in methanolic potassium carbonate at 0° for 4 h proceeded smoothly. Reduction of the ester $\bar{8}$ by sodium borohydride in methanol at room temperature for 2 h, followed by oxidation⁸ of the resulting alcohol with *N*-chlorosuccinimide, dimethyl sulfide and triethylamine provided the aldehyde $\bar{10}$ [72.5 % from $\bar{8}$, ν_{\max} 2260, 1720 cm^{-1} , δ 9.67 (1H, s, CHO)]. Since the desired aldehyde $\bar{10}$ was in our hands, the extension of α - and β -side chains was carried out as described below. The β -side chain of the

Scheme 2



thromboxane molecule was introduced by condensation of λ_{10} with the sodium salt of dimethyl 2-oxo-heptylphosphonate⁹ in benzene at room temperature for 2 h. Reduction of the resulting enone λ_{11} [56.8 %, ν_{\max} 2260, 1700, 1670, 1625 cm^{-1} , δ 6.10 (1H, d, $J = 16$ Hz, olefinic proton), 6.60 (1H, d, d, $J = 16, 8$ Hz, olefinic proton), m/e 261 (M^+)] was carried out using sodium borohydride in methanol at 0° to afford the allyl alcohol λ_{12} as a mixture of diastereoisomers [in quantitative yield, ν_{\max} 3600 ~ 3200, 2260 cm^{-1} , δ 5.70 (1H, d, d, $J = 16, 2$ Hz, olefinic proton), 5.33 (1H, d, $J = 16$ Hz, olefinic proton), 4.57 ~ 3.83 (4H, m, C_9H , $C_{11a}H$, $C_{15}H$, OH)]. Without separation of this mixture, the hydroxy group of λ_{12} was protected as its tetrahydropyranyl ether. Reduction of λ_{13} with diisobutylaluminium hydride (6 eq.) at -60° for 4 h, followed by a treatment of the mixture with saturated ammonium chloride solution produced the aldehyde λ_{14} [ν_{\max} 1725 cm^{-1} , δ 9.87 (1H, s, CHO)]. The Wittig reaction of the aldehyde λ_{14} with the ylide, derived from 5-triphenylphosphoniopentanoic acid, in dimethyl sulfoxide gave a mixture of C-15 diastereoisomeric acids λ_{15} [50.2 % from λ_{14} , ν_{\max} 1700 cm^{-1} , δ 9.73 (1H, br s, CO_2H , exchanged with D_2O), 5.76 ~ 5.0 (4H, m, olefinic protons), m/e 333 ($M^+ - 101$)], after purification on silica gel column chromatography. Cleavage of the tetrahydropyranyl group with acetic acid-water-tetrahydrofuran (20 : 10 : 3) at 40° , followed by separation of C-15 epimers by preparative tlc ($CHCl_3 - MeOH$, 9.5 : 0.5) afforded the desired acids λ_{16} and its C-15 epimer λ_{17} (ca. 1 : 1) [λ_{16} , ν_{\max} 3600 ~ 3200, 1710 cm^{-1} , δ 5.68 ~ 5.23 (4H, m, olefinic protons), 5.30 ~ 4.93 (2H, CO_2H , OH , exchanged with D_2O), 4.53 ~ 3.90 (3H, m, C_9H , $C_{11a}H$, $C_{15}H$), m/e 332 ($M^+ - 18$); λ_{17} , ν_{\max} 3600 ~ 3200, 1710 cm^{-1} , δ 5.63 ~ 5.23 (4H, m, olefinic protons), 5.33 ~ 5.03 (2H, CO_2H , OH exchanged with D_2O), 4.53 ~ 3.90 (3H, m, C_9H , $C_{11a}H$, $C_{15}H$), m/e 332 ($M^+ - 18$)]. The more polar compound was tentatively assigned the (15S) natural configuration^{5,9,10} by comparison with mobility on tlc plate (Rf 0.35 on silica gel with $CHCl_3 - MeOH$ 9.5 : 0.5; Rf 0.39 for less polar compound). In general, this fact has been observed in the field of prostaglandins.

The synthetic method described herein would provide a versatile method for stable thromboxane analogues which involve another heteroatom such as nitrogen and sulphur at the position of bridge-head.

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References and notes

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