SYNTHESIS OF THROMBOXANE A_2 ANALOGUE (±)-(9, 11),(11, 12)-DIDEOXA-(9, 11a)-OXA THROMBOXANE A_2

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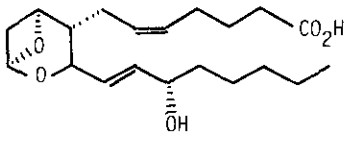
Summary A synthesis of the thromboxane A_2 analogue, (±)-(9, 11),(11, 12)-dideoxa-(9, 11a)-oxa-thromboxane A_2 (TXA_2) starting from the exo-adduct 3 of meleic anhydride and furan is described.

Thromboxane A_2 (TXA_2) generated by incubation of human blood platelet and the prostaglandine H_2 (PGH_2)[1,2] is an extremely labile substance with potent blood platelet aggregating and vasoconstrictor properties.[3,4] Samuelsson et at.[1] assigned its structure to be 1 on the basis of several trapping experiments and physiological property, although the whole structure of TXA_2 has not yet been confirmed directly. Since TXA_2 possesses an interesting spectrum of biological activity coupled with its lability, synthetic chemists have focussed on obtaining the stable TXA_2 analogues.[5] Here we wish to report the total synthesis of the stable TXA_2 analogue 2 starting from the exo-adduct 3 of maleic anhydride and furan.

Scheme 1



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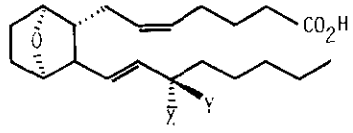


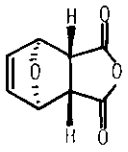
2 X=OH; Y=H

16 X=H; Y=OH

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° [95.3 %, ν_{max} 1760

cm^{-1}, m/e 154 (M^+)]. Treatment of 5 with potassium cyanide in dimethyl sulfoxide at 190° for 4.5 h gave the cyanated carboxylic acid 6. Without further purification, the crude carboxylic acid 6 was treated with diazomethane to afford the corresponding α-methyl ester 7,[7] mp 88 ~ 89° [62.7 % from 5, ν_{max} 2260, 1725 cm^{-1}, δ 3 75 (3H, s, OCH_3), m/e 195 (M^+)]. Epimerisation of the α-isomer 7 to the β-isomer 8,[7] mp 65 ~ 67° (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 8 by sodium borohydride in methanol at room temperature for 2 h, followed by oxidation[8] of the resulting alcohol with N-chlorosuccinimide, dimethyl sulfide and triethylamine provided the aldehyde 10 [72.5 % from 8, ν_{max} 2260, 1720 cm^{-1}, δ 9.67 (1H, s, CHO)]. Since the desired aldehyde 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



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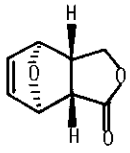

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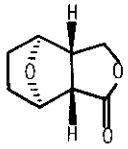

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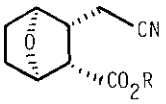
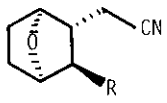
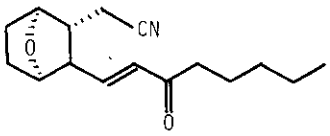


6 R=H
7 R=Me



8 R=CO_2Me
9 R=CH_2OH
10 R=CHO



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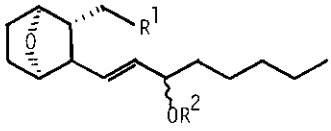

12 R^1=CN; R^2=H
13 R^1=CN; R^2=THP
14 R^1=CHO; R^2=THP
15 R^1=  ; R^2=THP

thromboxane molecule was introduced by condensation of 10 with the sodium salt of dimethyl 2-oxo-heptylphosphonate[9] in benzene at room temperature for 2 h. Reduction of the resulting enone 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^o to afford the allyl alcohol 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, $C_9\underline{H}$, $C_{11a}\underline{H}$, $C_{15}\underline{H}$, $O\underline{H}$)]. Without separation of this mixture, the hydroxy group of 12 was protected as its tetrahydropyranyl ether. Reduction of 13 with diisobutylaluminium hydride (6 eq.) at -60^o for 4 h, followed by a treatment of the mixture with saturated ammonium chloride solution produced the aldehyde 14 [ν_{max} 1725 cm^{-1}, δ 9.87 (1H, s, $C\underline{H}O$)]. The Wittig reaction of the aldehyde 14 with the ylide, derived from 5-triphenylphosphoniopentanoic acid, in dimethyl sulfoxide gave a mixture of C-15 diastereoisomeric acids 15 [50.2 % from 12, ν_{max} 1700 cm^{-1}, δ 9.73 (1H, br s, $CO_2\underline{H}$, 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^o, followed by separation of C-15 epimers by preparative tlc ($CHCl_3$ - MeOH, 9.5 : 0.5) afforded the desired acids 2 and its C-15 epimer 16 (ca. 1 : 1) [2, ν_{max} 3600 ∿ 3200, 1710 cm^{-1}, δ 5.68 ∿ 5.23 (4H, m, olefinic protons), 5.30 ∿ 4.93 (2H, $CO_2\underline{H}$, $O\underline{H}$, exchanged with D_2O), 4.53 ∿ 3.90 (3H, m, $C_9\underline{H}$, $C_{11a}\underline{H}$, $C_{15}\underline{H}$), m/e 332 (M^+ - 18); 16, ν_{max} 3600 ∿ 3200, 1710 cm^{-1}, δ 5.63 ∿ 5.23 (4H, m, olefinic protons), 5.33 ∿ 5.03 (2H, $CO_2\underline{H}$, $O\underline{H}$ exchanged with D_2O), 4.53 ∿ 3.90 (3H, m, $C_9\underline{H}$, $C_{11a}\underline{H}$, $C_{15}\underline{H}$), 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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