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SYNTHESIS OF A STABLE ANALOGUE OF THROMBOXANE A_1

(±)-9a-HOMO-(11,12)-DEOXA-(11,12)-METHYLENE THROMBOXANE A_1

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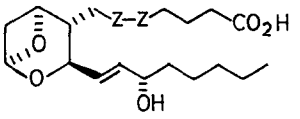
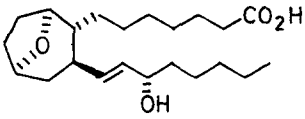
Summary: The thromboxane A_1 (TXA_1) analogue (1) has been synthesised from the ketone (2).

Thromboxane A_2 (TXA_2), an unstable ($t_{\frac{1}{2}}$ 32 sec. at 37°) metabolite of the prostaglandin endoperoxides, has potent blood platelet aggregating and vasoconstrictor properties.[1] Thromboxane A_1 (TXA_1) however, is not synthesised from its corresponding prostaglandin endoperoxides by human platelet microsomes,[2] and its occurrence has not been reported. We report herein the first synthesis of a stable analogue of this biologically elusive thromboxane.



TXA_1: Z–Z = CH_2–CH_2

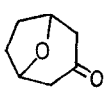
TXA_2: Z–Z = cis-CH=CH



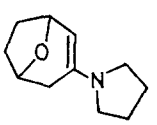
(1)

The starting bicyclic ketone (2)[3] was prepared in 51% overall yield, using a modification of the procedure of Hoffmann and Iqbal,[4] by the triethyl borate-zinc promoted cycloaddition of 1,1,3,3-tetrabromoacetone to furan, immediately followed by reductive debromination (Zn-Cu couple, NH_4Cl, CH_3OH) and then catalytic hydrogenation (10% Pd/C).

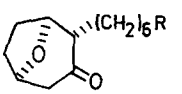
The pyrrolidine enamine (3) [ν_{max} 3050, 1630 cm^{-1}; $\delta(CDCl_3)$ 4.51 (2H,bcm), 4.37 (1H,d,J=5Hz), 2.98 (4H,m), 2.68 (1H,d of d, J=12Hz,5Hz)] of (2) was alkylated with the THP ether of 7-bromoheptanol to give stereospecifically the desired *exo*-alkylated ketone (4) [ν_{max} 1710 cm^{-1}; $\delta(CDCl_3)$



(2)

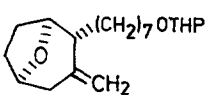


(3)



(4) R = CH_2OTHP

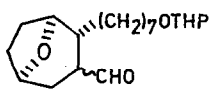
(5) R = CO_2CH_3



(6)

4.66 (1H,bt,J=5Hz), 4.56 (1H,bs), 4.44 (1H,bd,J=6Hz), 2.77 (1H,d of d,J=16Hz,6Hz); M^+ m/e 324.2308]. The *exo*-stereochemistry of (4) was unambiguously assigned from NMR spectral data, and was confirmed by an X-ray crystal structure of the methyl ester (5), prepared by the same method from the enamine (3).

Addition of *N*-methylphenylsulphonimidoylmethyllithium[5] to the ketone (4), followed by treatment with aluminium amalgam and acetic acid in aqueous THF gave the alkene (6) [ν_{max} 3070, 1645 cm^{-1}; $\delta(CDCl_3)$ 4.75 (2H,m)]. Hydration (BH_3.THF/H_2O_2,$OH^{\ominus}$) and then pyridinium chlorochromate oxidation of (6) gave a *cis-trans* (8:3) mixture of aldehydes (7) [ν_{max} 1725 cm^{-1}; $\delta(CDCl_3)$ 9.80, 9.65 (1H,2s)]. Isomerisation of (7) with 1,5-diazabicyclo[4.3.0]nonane (DBN) in dichloromethane gave predominantly the *trans*-isomer (*cis:trans* ratio 3:7), expected from steric considerations to be the thermodynamically more stable isomer. The *trans*-isomer of (7) [$\delta(CDCl_3)$ 9.65 (1H,s)] was separated by chromatography (silica gel, acetone:40-60° petroleum 1:25) and immediately used in a Horner-Wittig reaction with dimethyl (2-oxoheptyl)phosphonate to give the enone (8) [ν_{max} 1690, 1670, 1625, 980 cm^{-1}; λ_{max} (EtOH) 230 nm (ε=10,000); $\delta(CDCl_3)$ 6.77 (1H,d of d,J=16Hz,6Hz), 5.98 (1H,d of d,J=16Hz,1.5Hz), 4.56 (1H,bs); M^+ m/e 434.3408].



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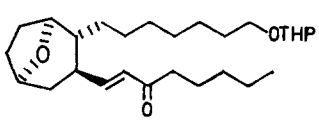
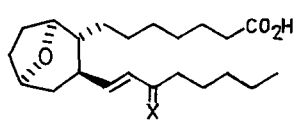


(8)



(9) X = O

(10) X = OH, H

(1) X = OH, H

Hydrolysis of the THP ether of (8) with 2M hydrochloric acid in ethanol (1:16) and oxidation of the resulting alcohol with pyridinium dichromate in DMF gave the enone-acid (9) [ν_{max} 2500-3600, 1710, 1670, 1625, 985 cm^{-1}] which on reduction with lithium tri-*sec*-butylborohydride (L-selectride) in THF at 0° gave the TXA_1 analogue (1) and its 15-hydroxy epimer (10) as a mixture of diastereoisomeric alcohols [ν_{max} 2400-3600, 1710, 975 cm^{-1}; $\delta(CDCl_3)$ 4.9-5.75 (4H,bcm), 4.35 (2H,bs), 4.08 (1H,bq,J=6Hz), 1.05-2.75 (28H,bcm), 0.89 (3H,t,J=6Hz); M^+ m/e 366].

Preliminary pharmacological studies with the mixture of (1) and (10) indicated that it had weak TXA_2-like properties with respect to vasoconstriction, but had no effect on blood platelet aggregation.

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